

LEKAN, DEBORAH ANN, Ph.D. *Frailty in Hospitalized Adults*. (2013)  
Directed by Dr. Debra C. Wallace. 393 pp.

The purpose of this cross-sectional, retrospective, descriptive study was to characterize frailty in hospitalized adults 55 years of age and older admitted to medical units at one large academic medical center during a 15-month time frame and determine if level of frailty on admission predicted length of stay (LOS) and 30-day readmission. Frailty is a syndrome characterized by multisystem physiologic dysregulation due to intrinsic and extrinsic stressors resulting in decreased compensatory reserve and ability to effectively respond to destabilizing health events. Stressors associated with hospitalization may increase risk for frailty or accelerate its development. Frailty is a significant concern as it is associated with morbidity, functional decline, long LOS, readmission, institutionalization, and mortality. There is scant research on frailty in acutely-ill hospitalized adults, especially those  $\geq 65$  years of age. Understanding frailty in this population is imperative because frailty is potentially preventable, treatable, and reversible. Frailty was operationalized as 14 evidence-based frailty components defined by 26 indicator variables. Frailty components were Nutrition, Weakness, Fatigue, Chronic Pain, Dyspnea, Falls, Vision, Depression, Cognition, Social Support, low Hemoglobin, low Albumin, high C-reactive protein (CRP) or hs-CRP, and abnormal WBC count. Each frailty component was scored as one point if at least one indicator variable was present on admission, and summed to derive a Frailty Score, where a higher Frailty Score suggests greater level of frailty (range, 0 to 14). Sociodemographic, clinical, and laboratory data were retrieved from the electronic medical record through web-based

data query tools and record review ( $N = 278$ ). Mean age was 70.2 ( $SD = 1.3$ ; range, 55–98), slightly over half were female, 64% were White, one-third were Black. The mean comorbidity count was 13 ( $SD = 4.56$ ; range, 1–26) and medication count was 12 ( $SD = 5.2$ ; range, 0–31). The most prevalent frailty components ( $> 81\%$ ) were Fatigue, Weakness, Nutrition, Hemoglobin, Albumin, and CRP or hs-CRP. The mean Frailty Score was 9.03 ( $SD = 1.98$ ; range, 2–13). Multiple linear regression was performed with 20 predictor variables and the Frailty Score and then with 14 of the 20 predictor variables that were significant in bivariate linear regression with the Frailty Score using the ENTER and STEPWISE method. All multiple regression models yielded seven significant predictor variables. Six predictors were common to all models: comorbidity, acute pain, ADL assistance, urinary incontinence, Braden Scale score, current tobacco use. In multiple regression with 20 predictors, age was a significant predictor however in multiple regression using ENTER and STEPWISE for 14 predictors, female gender was significant but not age. Results from STEPWISE regression yielded seven significant predictors that explained 27% of the variance in the Frailty Score (adj.  $R^2 = .266$ ,  $df(14, 263)$ ,  $F = 8.163$ ,  $p = .000$ ). Mean LOS was 9.92 days ( $SD = 9.58$ ; range, 1–72; median, 7; mode, 5). Simple linear regression for the Frailty Score and  $\log^{10}$  transformed LOS was statistically significant (adj.  $R^2 = .090$ ,  $df(1, 276)$ ,  $F = 29.293$ ,  $p = .000$ ). Twelve percent experienced 30-day readmission. Logistic regression conducted for the Frailty Score and 30-day readmission was not statistically significant ( $X^2 = 4.121$ ,  $df(5)$ ,  $p = .532$ ;  $\beta$  coefficient = .100,  $df(1)$ , 95%  $CI = .913$ – $1.1337$ ,  $p = .307$ ). The Frailty Score characterized this hospitalized population as acutely ill with high comorbidity, symptom

burden, nutrition deficits and evidence of physiologic vulnerability and inflammation. Study findings have implications for nursing practice, interdisciplinary collaboration, education, research, and public policy.

Key words: frailty, stress, hospitalization, elderly, middle-aged, C-reactive protein, Braden Scale

FRAILTY IN HOSPITALIZED ADULTS

by

Deborah Ann Lekan

A Dissertation Submitted to  
the Faculty of The Graduate School at  
The University of North Carolina at Greensboro  
in Partial Fulfillment  
of the Requirements for the Degree  
Doctor of Philosophy

Greensboro  
2013

Approved by

Debra C. Wallace  
Committee Chair

---

© 2013 Deborah Ann Lekan

APPROVAL PAGE

This dissertation, written by Deborah Ann Lekan, has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Committee Chair Debra C. Wallace

Committee Members Jie Hu

Eileen M. Kohlenberg

Heather E. Whitson

July 11, 2013  
Date of Acceptance by Committee

June 17, 2013  
Date of Final Oral Examination

## ACKNOWLEDGMENTS

First and foremost I would like to acknowledge the contributions of my dissertation chair and committee who provided ongoing guidance, encouragement, and expert advice as I progressed on this scholarly journey. I extend deep appreciation to my chair, Debra C. Wallace, PhD, RN, FAAN, for her generosity of time, expertise, and goodwill, for traveling to meet with me at critical times to discuss conceptual and methodological issues to ensure that this research met high standards of quality, rigor, and clinical relevance, and laid the groundwork for future research. Dr. Wallace is a model of integrity. She appreciates differences among students as strengths and supports and capitalizes on those strengths by providing clear approaches to help students meet goals of scholarly work. I sincerely thank Jiu Hu, PhD, RN for introducing me to the national and global significance of health disparities and cultural meanings of health and illness since these topics significantly influenced my work. My interest in frailty at midlife came about from exposure to health disparities research and social determinants of health as contributors to frailty risk factors that develop over the life course. This perspective reflects core nursing values of justice, caring, beneficence, and duty, values that underpin this research and speak to nursing's social responsibilities. I am grateful to Eileen M. Kohlenberg, PhD, RN for joining my committee at a crucial time and providing guidance about measurement of psychosocial-spiritual domains of frailty in hospitalized adults. This area is understudied in frailty research. In memoriam, I honor committee member Carolyn Blue, PhD, RN who was known for her unconditional

support of students and for the enthusiasm and joy she exuded in her teaching and interpersonal interactions. Dr. Blue's expertise in health promotion models influenced my conceptualization of frailty as a life-course phenomenon. She will always be admired and fondly remembered. Heather Whitson, MD, a renowned expert in geriatric medicine and frailty at Duke University School of Medicine, Division of Geriatrics, significantly influenced how frailty was defined in this study. This study builds on prior research and clinical practice collaborations and provides a new opportunity to study frailty and develop practical tools for clinicians that promote interprofessional communication and care coordination for primary and secondary prevention. Dr. Whitson's advice on conceptual and methodological issues related to frailty in this population and how to overcome challenges in EMR data retrieval and secondary analysis enhanced the validity and scientific rigor of this study. I offer special thanks to Susan Silva, PhD, external statistical consultant, Duke University School of Nursing, who generously shared her time and expertise during many late night discussions. Dr. Silva provided invaluable assistance in data transformation and advice about statistical models for analysis. I attribute my keen interest in statistics to Professor Thomas McCoy, biostatistician, whose expertise guided me and my classmates in understanding concepts and methods using a repertoire of learning activities, humor, and patience to gain a solid foundation.

I extend sincere appreciation to the Research Nurses at Duke University who assisted in data collection: Donna Harris, BSN, RN, Angel Barnes, BSN, RN, Chelsea Cocce, BSN, RN, and Ashley Roberston, BSN, RN. I am indebted to Michelle Mitchell whose expertise in working with large datasets, and procedures for accurate data entry

and validation was invaluable in construction of the dataset. Each of these individuals put forth tremendous effort under time sensitive circumstances. I am extremely grateful for the outstanding expertise of Richard Allen who provided hours of meticulous technical assistance in the final editing and formatting of this dissertation. The labyrinth of detailed specifications was navigated with his expert guidance and assistance.

I would like to acknowledge important research collaborations during my doctoral program with Bradi Grander, PhD, RN, FAAN, FAHA, Duke University Heart Center and Duke Translational Nursing Institute, Duke School of Nursing and Karen Alexander, MD, Duke University Medical Center. Through these collaborations, I was able to conduct two pilot studies and a secondary data analysis on fatigue and other symptoms related to frailty in hospitalized adults with cardiovascular disease. As a result of these experiences, I became better prepared in the research process. To my colleagues, Kirsten Corazzini, PhD and Eleanor McConnell, PhD, RN, APRN-BC, I thank you for supporting my aspirations and goals and encouraging me to consider different perspectives for focusing my research and staying on track. I would like to acknowledge several esteemed mentors who significantly influenced my nursing career and doctoral study: Rosan Hutter, MSN, RN, Carol Hogue, PhD, RN, FAAN, Lois Evans, PhD, RN, FAAN, Mary H. Palmer, PhD, RN, FAAN, Ruth Anderson, PhD, RN, FAAN, Peggy Chinn, PhD, RN, FAAN, Sharon Elliott-Bynum, PhD, RN, and many others. Thank you for inspiring possibilities I would otherwise not have imagined and encouraging my continued growth.

I could not have been more fortunate than to have had classmates who were highly experienced and gifted in so many diverse ways. We quickly formed a bond that

sustained us throughout the program and challenged each of us to exceed expectations knowing that we were all invested in each other's success. I know each of my classmates will make important, meaningful contributions in nursing that will benefit the health and well-being of people locally, nationally and globally and advance the science of nursing. I also honor the memory of classmate, Darlene Street, PhD, RN whose extraordinary research I learned about during monthly breakfast meetings at a local diner when she was finishing her dissertation. The mutual support energized us both. I cherish her spirit, faith, commitment to excellence, and reflections on the meaning of ones' life journey.

To my family, I offer my deepest gratitude for your unfailing support, understanding, and caring during a time in life that seemed like an eternity. I could always count on my mother, Betty Lekan, sisters, Susan and Mary, and brother, Alan to check in on me, ask about my studies, boost my spirits, and be sure I was thriving and not just surviving. My mother is a testament to healthy aging and resilience. Her lifelong optimism, faith, active, healthy lifestyle, and involvement in professional activities that empower women inspired me. Thank you for your angelic guidance. To my children, Mary and Michael, I cannot thank you enough and tell you about how important your support has been over the years; your text messages, phone calls, asking how the "D" was coming, offering study tips and sleep deprivation survival strategies. You both inspired me in so many ways and understood the sacrifices we all made in order for me to complete this work. We have a lot to catch up on. My father, Albert Lekan, was a man with an incredible work ethic who could do almost anything. He lived an active life with ESRD and dialysis. In his later years as his health declined, I learned what it meant to

become frail and live with diminishing resilience, autonomy, and continuity in life patterns, and to question the meaning of ones' life. I learned that there is no clear road map for frailty and many factors intersect along the way that alter the course of the aging trajectory and lead to incremental and progressive decline. However, the last stages of life can be joyful and peaceful. I consider myself blessed to have been a part of that experience. To Ron Rosich, thank you for your support, advice, and the many things you did to keep me afloat. Thank you, Bill Farley, for sharing travel adventures that brought balance to my life. Lynda Asato, dear friend and kindred spirit, thank you for being you, a model of inspiration. To Warren Kuhfeld, PhD, your enthusiasm for my work over the years has been meaningful. As high school classmates, who could have imagined we would find ourselves in North Carolina and somehow keep in touch as we pursued our goals. I know Professor McCoy and my classmates were impressed that you wrote the SAS code we used in class. Thanks for being there when I crossed the finish line.

My grandmother Mary Magdalene Sikora exemplified a model for aging well. She demonstrated resilience in times of adversity, an enduring sense of humor, genuine interest in others, keen memory for Hungarian family history, and a strong faith. She was kind, self-effacing and thrifty; her only unfulfilled wish was she never had a pair of red shoes when she was young. Her life was shortened by the debilitating trajectory and consequences of osteoporosis and frailty. In her memory, I dedicate this dissertation.

## TABLE OF CONTENTS

	Page
LIST OF TABLES .....	xii
LIST OF FIGURES .....	xiv
 CHAPTER	
I. INTRODUCTION .....	1
Overview .....	1
Features of Frailty .....	3
Hospitalization and Frailty .....	6
Purpose .....	7
Background .....	8
Historical Trends and Landmark Studies .....	8
Frailty Representation .....	14
Clinical Features .....	14
Natural History .....	16
Pathogenesis of Frailty .....	17
Significance .....	20
Aging Demographics .....	21
Hospitalization and Frailty .....	23
Adverse Consequences of Hospitalization .....	24
Nursing Home Discharge .....	26
Hospital Readmission .....	27
Frailty Assessment in Hospitalized Adults .....	27
Public Health Implications of Frailty .....	31
Definition of Frailty for this Study .....	33
Conceptual Framework .....	34
Introduction .....	34
The Biological-Psychological-Social (BPS) Model .....	34
Contemporary Application of the BPS Model .....	36
Stress Theory .....	36
Biologic Domain .....	39
Psychologic Domain .....	41
Social Domain .....	41
Spiritual Domain .....	43
Research Questions .....	43
Research Question 1 .....	43
Research Question 2 .....	44

Research Question 3 .....	44
Research Question 4 .....	44
Research Question 5 .....	44
Research Question 6 .....	44
Justification .....	44
Contributions of this Study .....	45
Chapter Summary .....	46
II. REVIEW OF THE LITERATURE .....	48
Introduction .....	48
Conceptual Model .....	55
Stress Theory .....	56
Homeostasis, Allostasis, and Allostatic Load .....	61
Demographic Data .....	64
Biologic Domain .....	64
Social Domain .....	110
Psychologic Domain .....	118
Defining Frailty .....	134
Frailty Perspectives and Prevalence .....	146
Phenotype for Physical Frailty .....	146
Deficit Accumulation Framework .....	152
Multidimensional Frailty Assessment .....	158
Comprehensive Geriatric Assessment (CGA) .....	166
Physical Performance Measures .....	167
Concordance of Frailty Definitions and Prevalence .....	174
Frailty and Hospitalized Adults .....	182
Health Care Delivery in Hospitals .....	202
Hospital Length of Stay and 30-Day Readmission .....	204
Summary of the Science of Frailty .....	206
Gaps in the Literature .....	208
Chapter Summary .....	214
III. METHODS .....	216
Sample .....	216
Setting .....	217
State Characteristics .....	217
Study Setting .....	219
Data Access .....	220
Demographic, Biologic, Psychologic, Social, and Spiritual Domains .....	223
Demographic Data .....	223

Biologic Domain.....	224
Psychologic Domain.....	228
Social Domain.....	228
Spiritual Domain.....	229
Frailty Components, Indicator Variables, and Measurement .....	229
Characterization and Scoring of Frailty.....	230
Study Outcome Variables .....	231
Validity .....	231
Data Acquisition and Data Entry .....	235
Data Analysis.....	235
Sample Description, Data Distribution, and Missing	
Data .....	235
Power Analysis .....	236
Analysis.....	237
Research Questions.....	238
Research Question 1 .....	238
Research Question 2 .....	238
Research Question 3 .....	238
Research Question 4 .....	240
Research Question 5 .....	242
Research Question 6 .....	242
Protection of Human Subjects .....	243
Study Limitations.....	244
Chapter Summary .....	246
 IV. RESULTS .....	 247
Sampling Method and Population.....	247
Sample.....	247
Frailty Score.....	253
Research Question 1 .....	255
Research Question 2 .....	256
Research Question 3 .....	256
Research Question 4 .....	263
Multiple Linear Regression for Candidate Predictor	
Variables and Frailty Score .....	264
Multiple Linear Regression Using ENTER and	
STEPWISE Method.....	266
Comparison of the Multiple Regression Models .....	270
Research Question 5 .....	271
Research Question 6 .....	272
Chapter Summary .....	273

V. DISCUSSION .....	275
Frailty Components and the Frailty Score .....	277
Frailty Components and Health Status Variables .....	279
Demographic, Biological, Psychological, Social-Spiritual Variables and Frailty Score.....	289
Implications.....	293
Strengths .....	298
Limitations .....	299
Conclusion .....	302
Recommendations for Education, Practice, and Research.....	303
Education .....	303
Clinical Practice .....	308
Research.....	312
Public Policy .....	316
Chapter Summary .....	319
REFERENCES .....	323

## LIST OF TABLES

	Page
Table 1. Projections of the Population by Selected Age Groups and Sex for the U.S.: 2010–2050.....	22
Table 2. Definitions of Frailty.....	136
Table 3. Frailty in Hospitalized Adults.....	189
Table 4. Data Query to Construct the Study Sample Using Study Inclusion Criteria.....	222
Table 5. Frequency Count of Independent Hospital Encounters for the Sample ( $N = 690$ ).....	223
Table 6. Laboratory Assay Equipment and Reference Ranges for Plasma Biomarkers.....	227
Table 7. The 14 Frailty Components and 26 Indicator Variables ( $N = 278$ ).....	230
Table 8. Evidence for the Frailty Components and Indicator Variables.....	232
Table 9. Sample Characteristics for Demographic, Biologic, Psychologic, and Social-Spiritual Domains ( $N = 278$ ).....	248
Table 10. Frequency and Percent of the 26 Categorical Indicator Variables ( $N = 278$ ).....	254
Table 11. Frequency Count and Percent of the 14 Frailty Components in the Sample ( $N = 278$ ).....	255
Table 12. Tests for Association for 14 Categorical Candidate Predictor Variables for the Demographic, Biologic, Psychologic, and Social-Spiritual Domains and 14 Categorical Frailty Components ( $N = 278$ ).....	259
Table 13. Tests for Association between 14 Quantitative Continuous Candidate Predictor Variables and each of the 14 Categorical Frailty Components: Significant Spearman's $\rho$ Point Biserial Correlation $r_s$ and $p$ Value ( $N = 278$ ).....	261

Table 14. Multiple Regression $\beta$ Coefficients for the Frailty Score and 20 Categorical and Quantitative Continuous Candidate Predictor Variables ( $N = 278$ ) .....	265
Table 15. Multiple Regression Coefficients for Frailty Score and Seven Significant Predictor Variables ( $N = 278$ ).....	266
Table 16. Bivariate Linear Regression Coefficients for the Frailty Score and 20 Candidate Predictor Variables ( $N = 278$ ).....	267
Table 17. Multiple Regression Coefficients for Frailty Score and 14 Significant Predictor Variables using ENTER Method ( $N = 278$ ).....	269
Table 18. Multiple Regression Coefficients using STEPWISE Method for 14 Significant Predictor Variables and the Frailty Score ( $N = 278$ ).....	270

## LIST OF FIGURES

	Page
Figure 1. The Biologic-Psychologic-Social-Spiritual and Stress Model.....	39

## **CHAPTER I**

### **INTRODUCTION**

#### **Overview**

Frailty is an important concept in care of the elderly. Frailty is a clinical condition that presents in atypical and non-specific manifestations that transcend disease categories, functional impairment, and disability (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004). The terms frail and frailty have appeared in various types of literature since ancient times but it was not until the 1980s when frailty was acknowledged in the medical community and in scientific and popular publications (Hogan, MacKnight, & Bergman, 2003; Nash, 2008). Frailty was described as a multifactorial state of decline related to old age, disease, weakness, decline in cognitive and physical function, weight loss, and social isolation (Burnside, 1990, Ferrucci, Mahallati, & Simonsick, 2006; Fillit & Butler, 2009; Hogan et al., 2003; Phillipson, 2002). Prior to 1995, there were no publications indexed in MEDLINE for the MeSH terms frail or frailty (Nash, 2008).

Frailty is an enigmatic condition since it is not always visibly apparent thus the boundary between frail and nonfrail state is blurred (Bergman et al., 2007; Gealey, 1997; Grenier, 2002; Levers, Estabrooks, & Ross-Kerr, 2006; Markle-Reid & Browne, 2003). Although comorbidity, functional impairment, disability, and clinical features such as low body weight, muscle atrophy, weakness, fatigue, slow gait, poor balance, falls, and cognitive impairment are associated with frailty, frailty can be present without obvious

deficits. Therefore, frailty presents a complex clinical picture with a wide spectrum of ambiguous signs and symptoms and clinical manifestations.

Frailty is a significant concern among health care providers and researchers because there are no common diagnostic criteria, assessment methodologies, or evidence-based prevention and treatment guidelines (Bergman et al., 2007; Ensrud et al., 2007, 2008; Fried, Tangen, et al., 2001; Fried et al., 2005; Weiss, 2011). Frailty is associated with unanticipated complications that arise from intrinsic and extrinsic stressors such as acute illness, chronic disease exacerbation, adverse events (e.g., falls, infection, delirium, pain, malnutrition, dehydration, functional decline, pressure ulcers), diagnostic procedures, surgery, and pharmacologic and medical treatment (Afilalo et al., 2010; I. Brown, Renwick, & Raphael, 1995; Fried, Tangen, et al., 2001; Fulop et al., 2010; Gobbens, Luijckx, Wijnen-Sponselee, & Schols, 2010c; Hadley, Ory, Suzman, Weindruch & Fried, 1993; Hogan, 2006; P. O. Lang, Michel, & Zekry, 2009; Nowak & Hubbard, 2009; Walston et al., 2006). There has been increased attention to frailty because it is significantly associated with morbidity, debilitating symptoms, functional decline, disability, dependence, falls, institutionalization, and shortened life span, yet there are ways to reduce the burden of this condition (Abellan van Kan et al., 2010; Ahmed, Mandel, & Fain, 2007; Buchman, Wilson, Bienias, & Bennett, 2009; Karunananthn, Wolfson, Bergman, Béland, & Hogan, 2009; Levers et al., 2006; Markle-Reid & Browne, 2003; National Institute on Aging, 1991; Strandberg & Pitkälä, 2007).

### **Features of Frailty**

Current research indicates that frailty is a distinct clinical condition that increases with age but is neither a universal nor inevitable correlate of aging. However, frailty lacks specific, objectively identifiable and measurable indicators that are different from normal age-related changes and pathologic processes associated with disease. There is limited evidence about its antecedents, risk factors, precursor or subclinical conditions, pathogenesis, genetic or epigenetic contributors, and other possible correlates (Ahmed et al., 2007; Bergman et al., 2007; Lally & Crome, 2007). Frailty is characterized as a multidimensional clinical syndrome and non-specific state in which there are no individual or groups of etiologies identified that cause or facilitate its development (Ahmed et al., 2007; Inouye, Studenski, Tinetti, & Kuchel, 2007; Xue, 2011). There is no empirical evidence for a biologic or clinical marker, medical diagnosis, sign or symptom presentation, diagnostic test, or performance measure that defines frailty (Bergman et al., 2007; Fulop et al., 2010; Xue, 2011). Frailty is enigmatic and often not observable, evolves sub-clinically in those who appear healthy, dynamic and heterogeneous in its manifestations, and may remain undetected until an intrinsic or extrinsic stressor overcomes physiologic compensatory mechanisms that promote homeostasis (Ahmed et al., 2007, Bergman et al., 2007; Bortz, 2002; McEwen & Wingfield, 2010; Studenski et al., 2004; Yang & Lee, 2010). During the aging process, multiple neurohormonal mechanisms maintain homeostasis in the context of global diminishing biologic function and chronic exposure to stressors. Frailty becomes clinically apparent when physiologic processes and cellular functions are disrupted by the impact of interactions between

disease conditions, lifestyle behaviors, acute and chronic psychosocial stressors, and adverse environmental exposures (Ahmed et al., 2007; Gleib, Goldman, Chang, & Weinstein, 2007; Xue, 2011).

Early theories of frailty suggest that physiologic vulnerability is an individual trait but recent research suggests that interactions between normal biological aging changes, pathophysiologic processes, acute and chronic disease, and psychosocial and environmental factors are influential (Fedarko, 2011; Yang & Lee, 2010). Data from the Health and Retirement Study found substantial heterogeneity in the rate of biologic aging and accumulation of diseases, disabilities, and other deficits which suggests that multiple interacting factors contribute to frailty (Mitniski, Graham, Mogilner, & Rockwood, 2002; Mitniski, Song, & Rockwood, 2004). Development of frailty is not a linear process that is readily explained by age, disease, or disability. Risk for frailty may be related to loss of complexity in dynamic biologic processes that constantly make adjustments through highly integrated interactions of chemical mediators across multiple body systems that promote biologic function and homeostasis (Fried et al., 2009; Lipsitz, 2004; Lipsitz & Goldberger, 1992).

The natural history of frailty is unclear, but two patterns are described. The first pattern describes frailty as an insidious, covert process whereas the second pattern describes frailty as a subjectively observable and clinically apparent state. In the first description, non-specific, subclinical changes occur early in the development of frailty. Incremental deterioration in multiple body systems leads to decline in function and ability to effectively respond to and recover from intrinsic and extrinsic stressors. Over time, an

increasingly fragile homeostasis is acquiescent until an acute decompensating health event occurs resulting in worse than expected responses and outcomes (Ahmed et al., 2007; Bandinelli, Corsi, Milanese, & Vazzana, 2010; Bortz, 2002; Studenski et al., 2004). Frailty is associated with failure of functional homeostasis or the capacity to appropriately respond to stressors (E. Carlson et al., 1998).

In the second description, frailty advances as an ambiguous and poorly differentiated decline in various physiologic systems. Clinical manifestations emerge but often are not directly traceable to a specific disease. Whitson, Purser, and Cohen (2007) similarly characterized two types of frailty: physiologic frailty or Ph-frailty and full frailty or F-frailty. Ph-frailty portrayed a state of physiologic vulnerability with preserved physical and cognitive function, whereas F-frailty portrayed full-blown functional frailty, with observable and measurable clinical signs. F-frailty can be accompanied by functional limitations that reflect the interacting effects of normal aging, acute illness, chronic disease, medications, and psychological, social, and environmental factors. Features of these two types of frailty may overlap, reflecting a dynamic continuum of physiologic stability and instability. These portrayals broaden understanding of frailty as a condition that is distinct from morbidity and precedes disability in its early inception in some clinical situations (Whitson et al., 2007). Clinicians often rely on subjective assessment and clinical judgment to identify frailty, however, in risk assessment and clinical decision-making about medical or surgical treatment, subjective assessment may miss identifying individuals who are frail, since objective indicators would not be apparent (Bergman et al., 2007; Studenski et al., 2004). Consequently, unexpected

adverse events and poor outcomes are more likely occur due to the lack of opportunity to initiate protective or preventive strategies.

### **Hospitalization and Frailty**

Hospitalization is common in adults as they age. It is estimated that 40% of inpatient beds and 60% of critical care beds are occupied by persons over 65 years of age (Fulmer et al., 2002; Hall, DeFrances, Williams, Golonsky, & Schwartzman, 2010). Greater hospital rates in older adults is associated with higher rates of acute illness and chronic disease exacerbation, falls, trauma, surgery, adverse medication effects, and changes in cognition and physical function (Heppenstall, Hanger, & Wilkinson, 2009; Lichtenberg, MacNeill, Lysack, Bank, & Neufeld, 2003; Campbell, Seymour, & Primrose, 2004). Research is sparse on frailty in acutely ill hospitalized adults. However, existing evidence indicates that hospitalized older adults who are frail experience worse outcomes compared to persons who are not frail (Afilalo et al., 2012; Anpalahan & Gibson, 2007; Boyd, Xue, Simpson, Guralnik, & Fried, 2005; C. J. Brown, Williams, Woodby, Davis, & Allman, 2007; Callen, Mahoney, Wells, Enloe, & Hughes, 2004).

Substantial literature describes the deleterious effects of hospitalization in older adults (Creditor, 1993; Lafont et al., 2011; Lefebvre et al., 1992; Mitty, 2010).

Hospitalization can lead to profound negative consequences beyond factors related to the reason for hospitalization. Hazards of hospitalization are well-documented: falls, injury, infection, delirium, dehydration, malnutrition, pressure ulcers, functional decline, prolonged recovery, new or worsening dependence, and mortality (T. M. Gill, 2010; T. M. Gill, Gahbauer, Han, & Allore, 2011; Hoogerduijn, Schuurmans, Duijnste, de Rooij,

& Grypdonck, 2007; de Saint-Hubert, Jamart, Boland, Swine, & Cornette, 2010). Importantly, functional decline may be integral in the development of frailty or influence its progression. Functional decline associated with acute illness or hospitalization in otherwise healthy, vigorous persons with or without chronic disease is more likely to be temporary with lower risk for irreversible functional decline, new dependence, and disability. The indeterminate clinical presentation of frailty suggests that frailty has a complex underlying pathogenesis that may be distinctly different from functional decline (Boltz, Resnick, Capezuti, Shuluk, & Secic, 2012; Callen, Mahoney, Grieves, Wells, & Enloe, 2004; Callen, Mahoney, Wells, Enloe, & Hughes, 2004; K. E. Covinsky et al., 2003; K. E. Covinsky, Pierluissi, & Johnston, 2011; Zisberg et al., 2011). However, frailty and functional decline are often inextricably linked as an etiologic factor, outcome, or correlate, thus attention to functional decline in hospitalized adults is crucial.

### **Purpose**

The purpose of this cross-sectional, retrospective, descriptive study was to characterize frailty in hospitalized adults 55 years of age and older admitted to general medicine, cardiology, or orthopedic services at one large academic medical center during a 15-month time frame and to determine if level of frailty on admission predicted hospital length of stay (LOS) and 30-day readmission. Understanding frailty in this population is imperative because frailty is potentially preventable, treatable, and reversible.

The conceptual framework for the study utilized the biological-psychological-social-spiritual (BPSS) model and stress theory to explore frailty as a multidimensional, multifactorial construct with dynamic interactions between the BPSS domains and

intrinsic and extrinsic stressors that impacts physiologic compensatory reserve and risk for frailty and adverse outcomes. Fourteen theory- and evidence-based frailty components were operationally defined for the study based on the conceptual model and data available from the electronic medical record (EMR). Frailty components included demographic, clinical, and laboratory data that included four plasma biomarkers empirically associated with inflammation, malnutrition, and frailty.

## **Background**

### **Historical Trends and Landmark Studies**

Heightened interest in frailty began in the 1970s as a result of demographic changes reflected in increased longevity and increasing numbers of older adults with multiple morbidity, functional limitations, disability, and cognitive impairment that led to higher utilization of emergency departments and increased hospitalizations (Butler, 1969; Vellas, Cestac, & Moley, 2012). Geriatrics was recognized as a specialty in medicine, nursing, and the social sciences which led to research that investigated biomedical and psychosocial aspects of aging and how to best care for an aging population (Bergman et al., 2007; Burnside, 1990; Gealey, 1997; Karunanathan et al., 2009; Levers et al., 2006; Markle-Reid & Browne, 2003; Vellas et al., 2012). Later interest in frailty was influenced by growing research on the physiology of aging or senescence, normal aging processes, differentiation of normal aging from disease and disability, atypical illness presentation, geriatric syndromes, comprehensive geriatric assessment, and interdisciplinary models for care (Isaks & Westendorp, 2003; Jarrett, Rockwood, Carver, Stolee, & Cosway, 1995; Palmore, 1977; Rockwood, Fox, Stolee, Robertson, & Beattie, 1994; Rockwood &

Hubbard, 2004; Rockwood & Mitnitski, 2007). Conventional stereotypes of growing old and being old were challenged and increasing heterogeneity among older adults was recognized, which spurred change in care delivery, health professional education, and public policy (Burnside & Touhy, 2006; Butler, 1969; Fillit & Butler, 2009; Lefevre et al., 1992; Matteson & McConnell, 1985; Institute of Medicine [IOM], 1991, 2008; Palmore, 1977; Vellas et al., 2012). Researchers and clinicians identified a subgroup of older adults portrayed as frail, a condition distinctly different from comorbidity and disability.

One of the first definitions of frailty was proposed by Brocklehurst (1985) who defined frailty as the breakdown of a dynamic balance between biomedical and social components due to decline in physiologic function and reduced reserve capacity that accelerates organ system deterioration, a cascade of health problems, and death. Since then, many definitions of frailty were proposed. National consensus conferences and professional geriatric organizations stimulated debate about frailty and frailty research advanced considerably. The general trend in frailty research and clinical practice was to define frailty according various indicators that included age, physical and cognitive function, activities of daily living (ADL) performance, disability status, comorbidity, and subjective appearance of weakness, feebleness, low body weight, and poor resilience.

In the 1980s and 1990s, early investigations of frailty proposed that frailty was a state of health in older adults with comorbidity and disability, and among the oldest-old (Burnside, 1990). Frailty was a state of physical and mental debilitation and functional impairment requiring substantial assistance from others for personal care, activities of

daily living (ADL), and social support in managing daily life (Gillick, 1989; Hadley et al., 1993; Shapiro & Tate, 1985; Tennstedt & McKinley, 1994; Woodhouse, Wynn, Baillie, James, & Rawlins, 1988). Having multiple biologic, physiologic, psychologic, and social deficits or impairments was considered salient as these contributed to dependence and adverse outcomes including worse disability, institutionalization, and mortality (Rockwood, Fox, Stolee, Robertson, & Beattie, 1994; Strawbridge, Shema, Balfour, Higby, & Kaplan, 1998; Winograd et al., 1991). Early frailty definitions included measures for physical function, nutrition, sensory ability, comorbidity, symptoms, medication, and others (Hamerman, 1999; Heuberger 2011). Some early definitions considered cognitive impairment a central feature of frailty (Burnside, 1990; M. Collins & Abeles, 1996; McDougall & Balyer, 1998; Parmelee, Lawton, & Katz, 1998; Tennstedt & McKinlay, 1994).

As research advanced, two major frailty perspectives emerged. The first perspective defined frailty as a uni-dimensional construct based on a biologic model for a frailty phenotype. The second model defined frailty as a multidimensional, multifactorial condition where frailty was the manifestation of the accumulation of deficits in biopsychosocial function and other factors, where the accrual of increasing numbers of deficits of any type over time increased risk for frailty, disability, and mortality. Both frameworks differentiated a subgroup of older adults as frail and at high risk for deleterious health events, poor recovery, and adverse outcomes. Other definitions of frailty in the literature vary widely and include any number of biopsychosocial and clinical or laboratory components.

**Frailty phenotype.** The first landmark study on frailty in the U.S. was conducted by the Cardiovascular Health Study (CHS) Collaborative Research Group (Fried, Tangen, et al., 2001) where frailty was defined as a syndrome based on a uni-dimensional biologic model for a frailty phenotype. Frailty was characterized by decreased compensatory reserve and poor resistance to stressors resulting in cumulative decline in cellular and organ function. Progressive physiologic breakdown across multiple organ systems leads to global physiologic dysregulation, increased vulnerability, ineffective response to stressors, and high risk for frailty and adverse outcomes (Fried, Tangen, et al., 2001).

The frailty phenotype is based on the premise that underlying physiologic disturbances manifest in integrated biologic and functional impairments. The CHS definition of frailty, often referred to as the Fried Frailty Index, included five domains and operational criteria: nutrition (unplanned weight loss of 15 pounds in past six months), energy (self-report of exhaustion, fatigue), physical activity (self-report of leisure time activity questionnaire); mobility (gait speed, timed four meter walk), and weakness (hand grip strength using dynamometer). According to the frailty phenotype, having three of the five criteria suggested a frail state, one or two criteria, an intermediate or pre-frail state, and no criteria, a robust, nonfrail state. The CHS frailty definition was validated in the CHS cohort of community-living older adults ( $N = 5,317, \geq 65$  years; Fried, Tangen, et al., 2001). The frailty criteria theoretically relate to a cycle of frailty that reflects declining physiologic complexity, energetics, compensatory reserve, and homeostasis. The Fried Frailty Index has been validated in numerous epidemiologic and cohort studies although exact replication of the five criteria has been inconsistent.

Research has expanded the Fried Frailty Index to include biopsychosocial constructs such as cognition, mood, social function, aerobic capacity, insomnia, nutrition, and physiologic biomarkers to improve sensitivity in case-finding and prediction of outcomes (Afilalo, Karunanathan, Eisenberg, Alexander, & Bergman, 2009; Afilalo, et al., 2012; Ávila-Funes et al., 2008; Bartali et al., 2006; Boxer, Wang, Walsch, Hager, & Kenny, 2008; Cawthon et al., 2007; Gobbens, Luijckx, Wijnen-Sponselee, & Schols, 2010a, 2010b; Gobbens et al., 2010c; Gruenewald, Seeman, Karlamangla, & Sarkesian, 2009; Rothman, Leo-Summers, & Gill, 2008; Vaz Fragoso, Gahbauer, Van Ness, & Gill, 2009). The Fried Frailty Index is a parsimonious tool with good psychometric properties in community populations and is relevant in clinical practice and research.

**Deficit accumulation.** The second framework was advanced by Rockwood and others (1994) who proposed the concept of deficit accumulation based on Brocklehurst's (1985) conception of frailty as a model of breakdown. A balance between biological and psychosocial components represents complex, dynamic interactions that affect independence and function. When intrinsic and extrinsic disturbances create an imbalance among these components, breakdown in the functioning of integrated body systems ensues leading to biopsychosocial dysfunction (Rockwood et al., 1994). According to this model, assets and deficits interact dynamically and can create instability. Even a small deficit can tip the balance and compromise the ability to live independently (Rockwood et al., 1994). An excess of deficits creates imbalance that leads to breakdown in multiple body and social systems and greater risk for frailty.

The deficit accumulation model has been tested in population-based studies using deficit counts of 20 to 90 (R. R. Cohen et al., 2012; Hastings, Purser, Johnson, Sloane, & Whitson, 2008; Kulminski et al., 2007; Mitniski, Graham, et al., 2002; Rockwood , Hogan, & MacKnight, 2000; Rockwood et al., 2004, 2005; Rockwood, Song, & Mitniski, 2011). The accumulation of any type of deficit created a physiologic burden. Individual deficits were not weighted however mathematical models were used to compute risk for disability, mortality, and level of frailty. This model is limited in determining frailty prevalence and translating data into practical approaches for clinical care. However, the deficit accumulation framework has been widely used in public policy and administrative sectors to assess population frailty to project and analyze resource needs, utilization, and costs. The deficit accumulation framework has included different numbers and types of deficits, incorporated comprehensive geriatric assessment and performance measures, and utilized simpler mathematical computations to assess frailty trajectories and outcomes in populations (Jones, Song, Mitniski, & Rockwood, 2005).

More recent research has adopted a multidimensional approach in defining frailty. Some frailty definitions incorporate elements of the frailty phenotype, deficit accumulation, biopsychosocial-spiritual and environmental factors and physiologic biomarkers. As a result, there is considerable diversity in frailty definitions, measurement, and study design. Cross-comparison studies where different frailty definitions were applied in a single study population report inconsistent results in frailty characterization, prevalence, and outcomes.

International conferences and expert panels that aimed to develop a consensus definition of frailty have not endorsed a frailty definition for use in clinical practice, research, and for administrative and public policy purposes. More recently, the Frailty Operative Definition-Consensus Conference Project reached agreement on six domains for frailty assessment: physical performance, gait speed, mobility, nutritional status, mental health, cognition, and biomarkers (Rodríguez-Mañas et al., 2012). However, an operational definition for key indicators of frailty was not specified. The I.A.N.A. Task Force and other groups recommend development of frailty screening tools that are quickly and easily administered in general practice and more detailed comprehensive assessment for at risk, high risk, and frail subgroups (Abellan van Kan, Rolland, Bergman, et al., 2008). There is agreement that assessment instruments will need to be designed based on the purpose, provider goals and objectives, characteristics of the sample and setting, and how the information will be used. Some frailty assessment instruments are more appropriate for research (e.g., Fried Frailty Index), for administrative and public health (e.g., deficit accumulation framework), and for clinical practice (e.g., FRAIL scale or single performance measure such as gait speed).

### **Frailty Representation**

#### **Clinical Features**

Frailty is a dynamic process described as fluctuations in homeostasis and shifting levels of vulnerability in response to intrinsic and extrinsic stressors (A. J. Campbell & Buchner, 1997; Slaets, 2006). Minor stressors that would be unlikely to provoke significant adverse sequela in healthy older persons with or without morbidity incite

acute biologic instability that precipitates a downward clinical trajectory in persons who are frail or are highly vulnerable (Ahmed et al., 2007; A. J. Campbell & Buchner, 1997; Fried Tangen, et al., 2001; Morley, Haren, Rolland, & Kim, 2006). Frailty is a complex condition that defies traditional biomedical diagnostic approaches (Cesari, 2011b). Clinical manifestations are ambiguous and present as a constellation of seemingly unrelated signs and symptoms which vary considerably among individuals. Thus, determination of frailty is by exclusion of other definable medical diagnoses (Cesari, 2011b; Gobbens et al., 2010a, 2010c; Gobbens, van Assen, Luijkx, & Wijnen-Sponselee, 2010; Levers et al., 2006; Morley et al., 2006; Yang & Lee, 2010).

Common clinical indicators of frailty are muscle wasting (sarcopenia), fatigue, weakness, exhaustion, poor endurance, low physical activity level, poor balance, abnormal gait, slow gait speed, falls, poor appetite or anorexia, malnutrition, weight loss, cachexia, cognitive impairment, depression, and delirium (Bergman et al., 2007; Fried, Tangen, et al., 2001; Hogan, 2006; Rockwood, 2005). Metabolic indicators include decreased bone mineral density, reduced lean muscle mass and quality, low serum cholesterol and hemoglobin level, elevated creatinine level, reduced insulin sensitivity, coagulation and immune system dysfunction, increased levels of serum inflammatory biomarkers such as C-reactive protein (CRP) or hs-CRP, white blood cell count (WBC), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF $\alpha$ ; De Martinis, Franceschi, Monti, & Ginaldi, 2006; Ershler, 2003; Ferrucci et al., 1999; Leng, Chaves, Koenig, & Walston, 2002; Sipe, 1995; Tak, Bakker, Slaet, & Rosmalen, 2009; Visser et al., 2005; Walston et al., 2002, 2006). Frailty is not always observable, thus differentiating persons

who are frail from those who are fit and robust is challenging and unreliable in clinical practice (Bergman et al., 2007). Examination of biomarkers as physiologic indicators of frailty may improve detection of subclinical vulnerability, risk status, and level of frailty.

### **Natural History**

Research has yet to validate etiologies of frailty, definitive predictors, or a typology based on different causal pathways. Frailty is often described as a progressive condition that follows an intractable, irreversible course, but longitudinal research indicates that frailty demonstrates a dynamic trajectory where level of frailty fluctuates under variable conditions with transitions between higher and lower levels of frailty (Buchman et al., 2009; Cesari, 2011b; T. M. Gill, Gahbauer, Allore, & Han, 2006; Puts, Lips, & Deeg, 2005a).

The incidence, prevalence, and severity of frailty increase with advancing age. Frailty has been viewed as a geriatric condition, thus the majority of research has been conducted in those who are older than 65 or 70 years of age. Advanced age is not a prerequisite or reliable predictor of frailty since many older adults are not frail (Ahmed et al., 2007; Fried, Tangen, et al., 2001; Heppenstall et al., 2009). Aging is associated with asynchronous, usually asymptomatic, incremental decline in structure and function of cells, organs, and systems that is accelerated by low levels of physical activity and poor nutrition (Bortz, 1993, 2002; Heuberger, 2011). Frailty has been proposed as an aberration of the aging process that is influenced by lifestyle habits, genes, and other factors (Bortz, 1989, 1993).

In the Cardiovascular Health Study, the prevalence of frailty was 3.2% in the 65 to 70 year old age group, 5.3% in the 71 to 74 year old age group, and 9.5% in the 75 to 79 year old age group (Fried, Tangen, et al., 2001). Several studies have examined frailty in middle-aged adults. In the Canadian Health and Aging Study ( $N = 14,713$ ), the prevalence of frailty was 2% in those  $\leq 30$  years of age, 22.4% in those  $\leq 65$  years, and 43.7% in those  $\geq 85$  years (Rockwood et al., 2011). At all ages, the 160-month mortality rate was lower among those who were fit compared to those who were frail: 2% versus 16% at 40 years of age; 42% versus 83% at 75 years or older, respectively (Rockwood et al., 2011). Santos-Eggimann, Cuénoud, Spagnoli, and Junod (2009) assessed frailty (using the Fried Frailty Index) in adults from 10 European countries ( $N = 18,227$ ) where 3.4-4.7% in the 55 to 64 year old age group and 15.3% to 18.7% in the 65 years of age and older group were frail. Alvarado, Zunzuneui, and Béland (2008) assessed frailty in adults age 60 years and older ( $N = 10,661$ ) using a modified Fried Frailty Index in seven Latin American and Caribbean cities. Frailty prevalence was not reported but frailty was demonstrated at all ages.

### **Pathogenesis of Frailty**

**Aging, inflammation, and frailty.** Chronic, low-grade inflammation is important in the pathogenesis of frailty. Aging and frailty are both associated with a pro-inflammatory state and chronic inflammation (S. S. Chang, Weiss, Xue, & Fried, 2012; McDermid, Stelfox, & Bagshaw, 2011; Yao, Li, & Leng, 2011). Aging is characterized by a chronic, low-grade inflammatory state, termed inflamm-ageing, which is influenced by genetics, exposure to infectious agents and lifelong antigenic load (De Martinis et al.,

2006; Franceschi et al., 2000). Balance between anti-inflammatory and pro-inflammatory processes that are protective in younger years are compromised with advancing age, leading to a pro-inflammatory state (McDermid et al., 2011). Inflamm-aging and a dysregulated pro-inflammatory state is strongly affected by stressors (De Martinis et al., 2006; Ferrucci et al., 2002; Franceschi et al., 2000).

Aging is accompanied by a two- to four-fold increase in circulating levels of inflammatory mediators (Krabbe, Pederson, & Bruunsgaard, 2004). Activation of inflammatory pathways is recognized by increased levels of IL-6 and its metabolite CRP, albumin, and WBCs (H. J. Cohen, Harris, & Pieper, 2003). Persistent dysregulation of physiologic systems due to chronic inflammation leads to altered levels of circulating biomarkers (Ferrucci et al., 2002; Gruenewald et al., 2009) and adverse consequences such as poor physical function, survival, and frailty (Rønning et al., 2010).

**Frailty, inflammation, and stress.** The relationships between frailty, age, inflammation, and chronic stress is an important area of research because mechanisms that provoke organ and cellular damage that leads to physiologic decline found in aging and frailty are poorly understood (H. J. Cohen et al., 2003; De Martinis et al., 2006; Kanapura & Ershler, 2009; Leng, Xue, Tian, Walston, & Fried, 2007). Frailty is significantly associated with chronic systemic low-grade inflammation (Cesari et al., 2004; H. J. Cohen et al., 2003; Phan, Alpert, & Fain, 2008; Puts, Visser, Twisk, Deeg, & Lips, 2005; Tracy, 2003; Walston et al., 2002). Low-grade chronic systemic inflammation may be responsible for functional decline in the elderly from the lifelong antigenic burden of inflamm-aging (De Martinis et al., 2006). Theories on the role of

inflammation in the development of frailty suggest that inflammation serves as a causal mechanism, a compensatory response to infectious disease, or a marker of pathophysiologic processes such as oxidative stress that leads to physiologic abnormalities (Hubbard & Woodhouse, 2010). Inflammation has been describes as part of the driving force toward frailty (Hubbard & Woodhouse, 2010).

Research indicates that detrimental effects of chronic stress precipitate maladaptive inflammatory responses that contribute to illness, disease, and frailty (Hubbard & Woodhouse, 2010; McEwen, 1993; Xue, 2011). Complex psychobiological mechanisms underlie physiologic responses to stressors that affect the immune, endocrine, hematologic, and coagulation systems resulting in chronic inflammation (Glaser & Kiecolt-Glaser, 2005; McEwen & Wingfield, 2010; Puts et al., 2005; Steptoe, Hamer, & Chida, 2007; Walston et al., 2002; Yao et al., 2011). The long term effect of low-grade chronic inflammation creates widespread systemic disruption in homeostasis and aberrant allostasis mechanisms. The cumulative damage from chronic inflammation leads to loss of cellular and organ function and system redundancies that are needed to activate physiologic processes for managing stressors (Abellan van Kan, Rolland, Bergman, et al., 2008). An enhanced proinflammatory state results from disruption or failure of mechanisms that balance proinflammatory and anti-inflammatory mediators that regulate normal immune function (McDermid et al., 2011; Walston et al., 2002; Yao et al., 2011). A persistent proinflammatory state leads to cellular damage and development of sarcopenia, muscle wasting, weakness, fatigue, reduced energy and

activity, malnutrition, weight loss, functional decline, and increased risk for accelerated aging, disease, and frailty (Franceschi et al., 2000, 2007; McDermid et al., 2011).

### **Significance**

Frailty is recognized as a significant public health concern as the numbers of those over the age of 65 years increase and the prevalence of chronic diseases among younger adults steadily grows. The human life span has increased as a result of decades of public health and medical advancements that reduced infant mortality and improved health and survival (Federal Interagency Forum on Aging-Related Statistics, 2010; Fries, 1988, 2005). However, contemporary societal factors introduced new risks for chronic disease, early disability, and frailty. Chronic diseases such as hypertension, heart disease, stroke, cancer, diabetes, arthritis, obesity, and respiratory disorders are becoming more prevalent and each is contributory to frailty risk factors and precursors (Bergman et al., 2007; Fries, 1988, 2005; Hackstaff, 2009; Jeune, 2002; Lally & Chrome, 2007; P. G. Lee, Cigolle, & Blaum, 2009; Mor, 2005; Phan et al., 2008; Pel-Little, Schuurmans, Emmelot-Vonk, & Verhaar, 2009; Woo, Goggins, Sham, & Ho, 2006; Fugate Wood et al., 2005). Social determinants such as low income or financial stressors, limited education, under- or unemployment, unhealthy lifestyle behaviors, exposure to daily life hassles and discrimination (ageism, racism, sexism, classism), and toxic living environments are each influential in increasing risk for frailty (Katz et al., 1983; Laditka & Laditka, 2002; Mullings, 2005; Szanton, Gill, & Allen, 2005; Szanton et al., 2008, Szanton, Seplaki, Thorpe, Allen, & Fried, 2010). Public policy and public health

initiatives will be necessary to effect changes in sociopolitical and healthcare systems in order to have the greatest impact on health status.

### **Aging Demographics**

The current U.S. population exceeds 314 million people and about one in eight, or 12.6%, is over 65 years of age. These estimates are expected to increase to 30% by 2050. The over 85 years age group continues to steadily increase with projections of almost 10 million by 2030, with the number of centenarians increasing dramatically (Federal Interagency Forum on Aging-Related Statistics, 2010; U.S. Census Bureau, 2008). In 2000, there were 50,454 centenarians (1 out of every 5,578) compared to 1990, where there were 37,306 centarians (1 out of 6,667; Hetzel & Smith, 2001). The male to female ratio has also changed, with increasing numbers of women in relation to men at advanced ages (Hetzel & Smith, 2001). Life expectancy projected at 65 years of age is 17.6 years in men and 20.3 years in women (American Fact Finder, 2012). Population projections are presented in Table 1. The proportion of racial and ethnic minority populations is also increasing. Currently, more than one third of the U.S. population belongs to a minority group. In 2010, Whites accounted for 74.3%, Hispanic, 15.1%, African American or Blacks, 12.3% Asian, 4.4%, and American Indian and Alaska Native, 0.8% (Administration on Aging, 2011).

Table 1

## Projections of the Population by Selected Age Groups and Sex for the U.S.: 2010–2050

Resident Population in Thousands, by Sex and Age									
	2010	2015	2020	2025	2030	2035	2040	2045	2050
Both sexes	310,233	325,540	341,387	357,452	373,504	389,531	405,655	422,059	439,010
45-64 yrs.	80,980	83,911	84,356	83,510	84,296	87,608	92,000	95,333	98,490
≥ 65 yrs.	40,229	46,837	54,804	63,907	72,092	77,543	81,238	84,456	88,547
≥ 85 yrs.	5,751	6,292	6,597	7,239	8,745	11,450	14,198	16,985	19,041
≥ 100 yrs.	79	105	135	175	208	239	298	409	601
Male									
45–64 yrs.	17,292	20,542	24,323	28,560	32,294	34,749	36,396	37,905	39,917
> 65 yrs.	17,292	20,452	24,323	28,560	32,294	34,749	36,396	37,905	39,917
> 85 yrs.	1,893	2,163	2,344	2,652	3,284	4,387	5,481	6,609	7,458
> 100 yrs.	15	21	29	40	51	62	81	114	172
Female									
45-64 yrs.	41,513	42,939	43,065	42,498	42,747	44,743	46,573	48,308	49,974
> 65 yrs.	22,937	26,295	30,481	35,346	39,798	42,794	44,842	46,551	48,630
> 85 yrs.	3,859	4,130	4,253	4,587	5,461	7,063	8,717	10,376	11,583
> 100 yrs.	65	84	106	134	156	177	217	295	429

Source: U.S. Census Bureau, 2008

Demographic data describing an increasing aging population has drawn attention to frailty in the health care and public policy sector since the incidence and prevalence of frailty and health care costs is expected to increase. Although many older adults experience some decline in physical, cognitive, and/or functional status at advanced ages, not all are destined to become frail (Molina-Garrido & Guillen-Ponce, 2010). Frailty may represent a proxy for chronologic age for many aspects of health status that are difficult to measure and interpret in adults with diverse morbidity, symptoms, and BPSS function (McDermid et al., 2011). How the needs of a diverse aging population will be met is of concern (Karunanathan et al., 2009; Morley et al., 2006; Szanton et al., 2005). A wide range of health and social services that emphasizes health promotion, prevention of disease and disability, and optimal management of chronic conditions will be required to achieve HP 2020 goals for increased active life expectancy and quality of life (Fries, 1988; Hackstaff, 2009; Healthy People 2020, 2013; Izaks & Westerdorp, 2003; Mor, 2005; Woo et al., 2006). Integration of comprehensive geriatric assessment and nursing and interdisciplinary team collaboration would facilitate identifying and coordinating care for the aging population that can improve chronic disease management, biopsychosocial function, and quality of life, and reduce preventable hospitalizations.

### **Hospitalization and Frailty**

Frailty is associated with increased odds for hospitalization. In the Women's Health Initiative-Observational Study, the largest population-based study to examine frailty, hospitalization for frailty and intermediate frailty was associated with odds ratios

(*OR*) of 2.0 (1.7-2.2) and 1.3 (95% *CI*, 1.2-1.5). These findings compare to data on men and women in the Cardiovascular Health Study (Fried, Tangen, et al., 2001).

### **Adverse Consequences of Hospitalization**

Hospitalization is associated with many intrinsic, extrinsic, and system-related stressors with significant life-altering and life-threatening consequences. Hospitalized adults are exposed to increased risk for adverse events and poor outcomes that develop rapidly with cascading detrimental effects (Graf, 2006; de Saint-Hubert et al., 2010). Many hospitalized older adults experience higher rates of surgical or treatment-related complications, falls, delirium, pressure ulcers, under-treated pain, malnutrition, and dehydration with detrimental consequences, a phenomenon described as cascade iatrogenesis (Potts et al., 1993; Thornlow, Anderson, & Oddone, 2009), but little is known about how to improve care to reduce these situations (Finlayson & Birkmeyer, 2001; Nalysnyk, Fahrback, Reynolds, Zhao, & Ross, 2003; T. N. Robinson, Wu, Stieglmann, & Moss, 2011; Rolfson et al., 1999; Zalon, 2004). Frailty is a strong independent predictor of ADL dependence, morbidity, worsening frailty, and mortality. In a study of hospitalized older women ( $N = 749$ ,  $\geq 65$  years), where 25% were frail at baseline, 56% developed ADL dependence at three-year follow up compared to 20% who were not frail at baseline (Boyd et al., 2005). In a prospective study in community older adults, transitions in frailty level associated with hospitalization, 88% had at least one frailty transition and 89.4% were hospitalized during 108-month follow-up ( $N = 754$ ,  $\geq 70$  years; T. M. Gill et al., 2011). At baseline, 26.6% were frail, 51.5% prefrail, and 22.9% nonfrail. The most common transition was from nonfrail to prefrail, and the least

common, frail to nonfrail. The risk for transition to a higher level of frailty increased with hospitalization. Transition from nonfrail to frail was uncommon in those who were not hospitalized. Hospitalization was strongly associated with mortality at all frailty levels.

Hospitalization is associated with prolonged activity restriction and immobility. Factors such as intravenous tubes, oxygen masks, catheters, wound dressings, cardiac monitoring electrodes, and devices limit mobility in addition to imposed restriction due to the medical condition. The detrimental pathophysiological, psychological, and functional impact of immobility has been well-described for decades (Fretwell, 1993; Harper & Lyles, 1988; Mahoney, 1998; Olson, Johnson, & Thompson, 1990). The cascading and interacting effects of activity restriction and immobility on physiologic function produce striking responses in all body systems. Risk for frailty is markedly increased in the context of immobility (J. E. Carlson et al., 1998; Heppenstall et al., 2009).

Immobility during hospitalization is an under-recognized clinical care issue with serious and potentially irreversible consequences (Boyd et al., 2005; C. J. Brown, Friedkin, & Inouye, 2004; Brown, Redden, Flood, & Allma, 2009; Callen, Mahoney, Wells, et al., 2004). Health care providers cite barriers to mobilizing acutely ill hospitalized older adults that can be insurmountable; however, proactive measures for early mobilization including bed mobility and progressive physical activity is uncommon in many clinical settings (Boltz et al., 2008a, 2008b; C. J. Brown et al., 2007; Callen, Mahoney, Grieves, et al., 2004). Functional decline is a significant consequence of hospitalization-associated immobility and is estimated to occur in 30% to 60% of older adults (K. E. Covinsky et al., 2003; K. E. Covinsky et al., 2011; T. M. Gill, Gahbauer,

Han, & Allore, 2009; Inouye, Bogardus, Baker, Leo-Summers, & Cooney, 2000; Lafont et al., 2011). Hospitalization is independently and significantly associated with new-onset ADL dependence, functional decline, and disability (Boyd et al., 2005; T. M. Gill, Allore, Gahbauer, & Murphy, 2010; Hirsch et al., 2006; Sager & Rudberg, 1998). The trajectory of functional decline may begin prior to admission due to acute illness or chronic disease exacerbation which may sensitize providers that admission functional status is also baseline status. Consequently, planned efforts for remobilization and rehabilitation may be deferred or delayed. The impact of acute illness or surgery would be expected to compromise mobility function and perhaps lead to slower recovery however without individualized, aggressive interventions for graded mobilization and re-conditioning, functional decline will worsen in many older adults. Therefore, despite resolution of the medical problems that precipitated hospitalization, the downward trajectory of functional decline will continue to worsen during hospitalization and continue after discharge (K. E. Covinsky et al., 2011). Research indicates that hospital-associated immobility and functional decline is significantly associated with failure to return baseline status and higher level of dependence and increased mobility and ADL limitations.

### **Nursing Home Discharge**

Hospitalization is associated with greater risk for nursing home discharge. Functional decline is often a critical factor that precipitates nursing home discharge (T. M. Gill et al., 2009). In a retrospective study of Medicare beneficiaries  $\geq 66$  years ( $N = 762,243$ ), 5.55% were living in a nursing home 6-months after discharge compared with 0.54% of non-hospitalized controls, often due to functional decline (Goodwin, Howrey,

Zhang, & Kuo, 2011). In a study of nondisabled community persons  $\geq 70$  years hospitalized and discharged to a nursing home within 46 months ( $N = 754$ ,  $n = 296$  who were admitted to a nursing home, nine-year follow up), the most common trajectory was discharge home with disability followed by discharge to a nursing home with disability (46.3%), discharge home without disability (27.4%), discharge home without disability (21.6%), and non-continuous disability in the nursing home (4.4%; T. M. Gill et al., 2009). Prior to hospitalization, 63.9% had no disability. Only 32.4% returned home at or above their pre-hospitalization functional status.

### **Hospital Readmission**

Hospitalization rates and readmission rates are high among older adults and many are potentially avoidable. In 2010, of 31 million Medicare beneficiaries, about 10 million (4%) were hospitalized. The 30-day all-cause readmission rate among those who were hospitalized was 19.2% at a cost of \$17.5 billion to the Medicare program (Centers for Medicare and Medicaid Services [CMS], 2012a). In a study of hospitalizations of Medicare and Medicaid beneficiaries ( $N = 1,571,920$ ), of 960,000 hospitalizations, 383,000 were potentially avoidable compared to 577,000 that were deemed unavoidable (Ouslander & Berenson, 2011). About 24% of nursing home discharges were readmitted within 30 days.

### **Frailty Assessment in Hospitalized Adults**

There is limited literature on frailty assessment in hospitalized adults. Since advanced age and physical signs and symptoms are not reliable indicators of frailty, it can be difficult to determine who is at risk for frailty or who is frail since frailty precursors

and risk factors are detected in midlife adults (Hubbard & Woodhouse, 2010; Shore & DeLateur, 2007; Xue, 2011). The heterogeneity among adults presents challenges since conventional assessments are not reliable in identifying frailty (Afilalo et al., 2009; Albert, Im, & Raveis, 2002; American Medical Association [AMA], 1990; Manton, 2008; Raphael et al., 1995; Woo et al., 2006; Yang & Lee, 2010). Most frailty research in hospitalized older adults (most often in surgical populations) utilized assessment tools or measures employed in frailty research in community older adults that may exhibit multiple morbidity and disability but are medically stable (Afilalo et al., 2012; Gharacholou et al., 2012, Hilmer, Perera, et al., 2009; Makary et al., 2010; T. N. Robinson et al., 2009; Robinson, Wallace, et al., 2011; Robinson, Wu, et al., 2011; Rønning et al., 2010). Assessment approaches in these populations are often non-transferable to the hospital setting in acutely ill, medically complex, and unstable patients. Research on frailty in hospitalized adults has primarily focused on older adults admitted for elective surgery to determine if frailty assessment identified patients who were more likely to experience post-operative complications, functional decline, disability, longer length of stay, institutionalization, and mortality. In a study of older adults 70 years of age and older admitted to a cardiology unit that compared the findings of two different frailty assessment models (Fried Frailty Index, deficit accumulation framework) and individual performance measures (gait speed, handgrip strength) found that frailty classification identified by the composite assessment models or individual performance measures significantly predicted six-month mortality (Purser et al., 2006). Gait speed was the strongest predictor of poor outcomes.

Emerging research in hospitalized populations indicates that frailty assessment augments traditional medical assessments for specific chronic conditions such as heart failure and multiple medical conditions (Cacciatore et al., 2005; Pilotto et al., 2012; T. N. Robinson et al., 2009) and preoperative risk assessment (Afilalo et al., 2012; N. A. Brown & Zenilman, 2010; Cleveland, 2010; R. R. Cohen et al., 2012; Dasgupta, Rolfson, Stolee, Borrie, & Speechley, 2009). Chronologic age and comorbidity have been relied upon as primary risk indicators, but they have not proven to be consistently stable predictors of complications and survival in older adults due to heterogeneity in the aging population. Biologic age is now viewed as a more reliable predictor of risk suggesting that other influential factors are not accounted for in standard risk assessment (Castle, Uyemura, Rafi, Akande, & Makinodan, 2005; Mitnitski, Graham, et al., 2002; Mitnitski, Mogilner, & Rockwood, 2001). Frailty assessment captures multidimensional factors that influence risk for poor outcomes, for example, tolerance of invasive procedures, toxic pharmacologic therapy, and high risk medical and surgical interventions (Afilalo et al., 2009). There is growing agreement that standard risk assessment tools fail to differentiate a subgroup of older adults who are at high risk for poor outcomes who may fare worse than expected compared to others who may be older and appear less resilient, but recover better than expected (Makary et al., 2010). Frailty assessment augments standard clinical tools to improve detection of patients who appear medically stable and do not score as high risk on standard risk assessments but unexpectedly experience complications and poor outcomes (Makary et al., 2010).

Less frequently studied for their influence on frailty in hospitalized adults are geriatric syndromes such as delirium, falls, functional decline, pain, fatigue, incontinence, poor appetite, malnutrition, sleep problems, pressure ulcers, and others (Ahmed et al., 2007; K. E. Campbell, 2009; C. C. Chen, Dai, Yen, Huang, & Wang, 2010; C. C. Chen, Yen, Dai, Wang, & Huang, 2011; P. G. Lee et al., 2009; Inouye et al., 2007; Lafont et al., 2011; Quinlan et al., 2011; Schwab, 2008). These syndromes may be present on admission or develop during hospitalization. Geriatric syndromes are associated with increased risk for frailty and adverse consequences related to new dependence, new morbidity and poor discharge health status, longer length of stay, nursing home discharge, long term institutionalization, and shortened life span. Since frailty is considered a syndrome, the extent to which other syndromes can be addressed concurrently as part of frailty assessment may improve detection and prevention since there is evidence of shared risk factors among these syndromes (K. E. Campbell, 2009; Donini, De Felice, Tagliaccica, De Bernardini, & Cannella, 2005; Inouye et al., 2007; Kane, Talley, Shamiliyan, & Pacala, 2011; Tinetti, Inouye, Gill, & Doucette, 1995).

Particular attention to functional decline in hospitalized adults is warranted since functional decline may be a primary etiologic factor in frailty and deleterious geriatric syndromes. Poor functional status on admission and excessive decline during hospitalization may signal high risk frailty status and alert providers to assess and initiate appropriate prevention and intervention (Hoogerduijn et al., 2007; Hoogerduijn, Schuurmans, Korevaar, Buurman, & de Rooij, 2010; de Saint Hubert et al., 2010). However, functional decline and frailty may be distinctly different. Although there can be

overlap in presentation and etiologic factors, frailty reflects global multisystem physiologic dysregulation and poor compensatory reserve whereas functional decline may be due to an immobility and various intrinsic and hospital-associated factors that may be self-limiting (Creditor, 1993; Lafont et al., 2011; Lefevre et al., 1992).

Differentiating frailty from functional decline would facilitate targeting treatment to address multifactorial features of these conditions (Afilalo et al., 2012; J. E. Carlson et al., 1998; de Saint-Hubert et al., 2010; Hilmer, Mager, et al., 2009; Pilotto et al., 2012; Sutton, Grimmer-Somers, & Jeffries, 2008).

Research is needed to characterize frailty in acutely ill hospitalized adults in different age ranges and at different time points during hospitalization (Boyd et al., 2005; Mitty, 2010; Rozzini, Frisoni, Franzoni, & Trabucchi, 2000). Most frailty research in hospitalized adults is focused on older adults 65 or 70 years of age and older (Afilalo et al., 2010, 2012; J. E. Carlson et al., 1998; Dasgupta et al., 2009; Freiheit et al., 2010; T. M. Gill, Allore, et al., 2010; Kristjansson et al., 2010; Makary et al., 2010; Pilotto et al., 2012; Purser et al., 2006; T. N. Robinson et al., 2009; Rønning et al., 2010). However, frailty indicators are detected in middle-aged adults (Pol et al., 2011). There are no evidence-based guidelines about frailty indicators that are predictive of adverse frailty trajectories and outcomes by different age strata or if frailty components should be normed by age, gender, race/ethnicity, or other factors (Heuberger, 2011).

### **Public Health Implications of Frailty**

Healthy People (HP) 2020 is an important U.S. public health initiative to advocate that people live long, healthy lives free of preventable disease, disability, injury and

premature death (Healthy People 2020, 2013). The HP 2020 objectives for older adults formulate a blueprint for healthy aging. Objectives relevant to frailty and this study are to increase the proportion of older adults who report confidence in managing their chronic condition, reduce the proportion of adults with moderate to severe functional limitations, increase the proportion of adults with physical or cognitive limitations to participate in physical activity, reduce the rate of pressure ulcer-related hospitalizations, and reduce the rate of emergency department visits due to falls (Healthy People 2020, 2013).

Research and clinical practice initiatives that address frailty are crucial to meeting HP 2020 objectives. Relying on factors other than chronologic age in public health planning will be necessary. Older age is associated with more chronic conditions but age of onset and disease severity varies. Medical expenditures for older adults with multiple chronic conditions are eight-times higher compared to those with few chronic conditions (Fries, 1988; IOM, 1991, 2001). Public health initiatives such as enhanced screening for frailty in hospitalized adults (Sutton et al., 2008), disease management and transitional care programs ,and community based health and social services are needed to facilitate effective self-management of chronic conditions, reduce symptom burden and disease exacerbation, decrease risk for preventable complications and disability, increase active life expectancy and quality of life, and prevent or delay frailty (Burke et al., 2001; Hamerman, 1999; Landi, Abbatecola, et al., 2010; Landi, Russo, et al., 2010; Morley, 2010; Ozaki, Uchiyama, Tagaya, Ohida, & Ogihara, 2007; Peterson et al., 2009; Raphael et al., 1995; Shore & DeLateur, 2007; Tennstedt & McKinlay, 1994; Wolff & Kasper, 2006; Woo et al., 2006). Frailty assessment, prevention, and intervention is needed to

reduce its incidence and prevalence and alleviate the burden it imposes at great cost to individuals, families and communities (Aggar, Ronaldson, & Cameron, 2010; Bergman et al., 2007; Healthy People 2020, 2013; Wolff & Kasper, 2006).

A greater understanding of frailty in the acutely ill hospitalized population is needed since research is lacking and hospitalization is a sentinel event that can precipitate or worsen frailty. Assessing frailty in adults 55 years of age and older is important since primary and secondary prevention holds greater potential for benefit at younger ages (Hackstaff, 2009; IOM, 1991; Peterson et al., 2009). Frailty can be halted, ameliorated, reversed, or its progression delayed with appropriate interventions (Heuberger, 2011). Hospitalization presents an opportunity to assess and intervene early in order to interrupt the frailty trajectory and initiate targeted interventions that maximize individual outcomes and health system indicators associated with cost and quality of care.

### **Definition of Frailty for this Study**

For this study, frailty was defined as a dynamic, multidimensional, multifactorial syndrome associated with poor compensatory reserve in response to intrinsic and extrinsic stressors and greater risk for the accumulation of deficits in biopsychosocial-spiritual function that leads to incremental or precipitous physiologic dysfunction and failure to effectively respond to and recover from destabilizing health events to restore homeostasis. Frailty arises from the interacting effects of age, chronic disease, symptom burden, functional limitations, disability, and other intrinsic and extrinsic biopsychosocial stressors that lead to poor outcomes (Bergman et al., 2007; Coles, 2004; Fried, Tangen, et

al., 2001; Fried et al., 2004; Geronimus, 2001; Hamerman, 1999; Hubbard & Woodhouse, 2010; Lally & Crome, 2007; Rockwood, 2005; Whitson et al., 2007).

## **Conceptual Framework**

### **Introduction**

This study was guided by a conceptual framework that links the biological-psychological-sociocultural-spiritual (BPSS) model and stress theory. The BPSS-Stress model framed frailty as a process that evolves across the life course in response to dynamic interactions occurring within the person and between the person and the environment. The BPSS-Stress model emphasizes holism where intrinsic and extrinsic factors that influence health status and well-being are inseparable. The BPSS-Stress model is appropriate for characterizing multidimensional, multifactorial aspects of frailty over time (Bowsher, Bramlett, Burnside, & Gueldner, 1993; Engel, 1977; Young, Frick, & Phelan, 2009; Zittel, Lawrence, & Wodarski, 2002).

### **The Biological-Psychological-Social (BPS) Model**

In the 1970s, the biological-psychological-social (biopsychosocial, BPS) model was introduced as an alternative to the biomedical model that dominated medical education and health care as scientific innovations increased and medical care became more specialized (Engel, 1977, 1981). The biomedical model emphasized the Cartesian separation of the mind and body and advocated new scientific knowledge about cellular pathology and posited causal relationships between signs, symptoms and disease (Main, Richards, & Fortune, 2000). Rapid advancement in science and technology was driven by reductionist cause-and-effect models in the study of disease delimited by separate organ

or body systems (Schwab, 2008). The notion of “one microbe-one illness” was promoted in medical education leading to specialization (Borrell-Carrió, Suchman, & Epstein, 2004, p. 578). Subsequent research, however, substantiates the complex inter-relationships within and across organs and body systems that depend on non-linear process for up-regulation and down-regulation of chemical mediators that maintain homeostasis. Research has demonstrated that disease, symptom burden, functional decline, and disability are due to biologic, psychological, and social factors and not the product of pathologic physiologic processes alone (Fried et al., 2009; Lipsitz, 2004; Lisitz & Goldberger, 1992; Main et al., 2000).

The BPS model is based on systems theory that identifies elements of a domain, how they are interrelated, and the significance of their integration in creating human wholeness (Engel, 1981). The person is viewed as a unique individual who functions within a social and cultural context that strongly influences the perception and meaning of illness and how to best manage its disruptive effects (Engel, 1977, 1981). The BPS model underscores the inseparability of the parts of the human experience from the whole person, and that the whole is greater than the sum of its parts. Engel (1981) asserted that the presence of a biological derangement does not reflect the meaning of that problem to the person or that the problem represents a state of illness. Illness and symptoms arise from interactions of diverse factors, where psychological factors can be more important determinants of an illness and its severity and course than can be explained from a biomedical perspective (Borrell-Carrió et al., 2004; Engel, 1977, 1981). The BPS model draws a distinction between disease and the person’s perception of the impact of disease

on their health, family and social network, and daily life. Upon its introduction, the BPS model was controversial as it signaled a paradigm shift from a focus on disease to a focus on health by acknowledging that psychological and social factors impact development of acute illness, chronic disease, and patterns of recovery.

### **Contemporary Application of the BPS Model**

The BPS model is described as a philosophy of clinical care and a guide for clinical practice. Borrell-Carrió et al. (2004) described the BPS model as a framework for understanding how illness and suffering impact the individual at multiple levels, from the molecular to the societal. Spirituality was included as a fourth domain. In practice, the BPS model continues to be relevant by providing a framework for understanding the patient's experience in order to determine more accurate diagnoses, provide humane, person-centered care, foster autonomy, and achieve better outcomes (Adler, 2009). The acronym BPSS was used in this study for the biologic-psychologic-social-spiritual model.

### **Stress Theory**

Stress is inherent in daily life and essential for healthy human function. Stress theory was first introduced by Hans Selye (1955) who defined stress as a “nonspecific response of the body to any demand” and developed a physiologic model called the General Adaptation Syndrome (GAS; Selye, 1974, p. 14). In early research, Selye proved that stress-induced breakdown in neurohormonal systems could lead to diseases of adaptation, such as heart disease and hypertension (Selye, 1974). The GAS focused on acute stress that activates the fight-or-flight response when a person confronts a perceived threat. Selye's focus on the pathophysiology of the stress response contributed new

knowledge about the biology of stress and the brain's role in physiological regulation of feedback between the brain and the body. This pioneering work introduced the importance of the mind-body connection (Schulkin, 2003) and broadened understanding of health and disease as inseparable from biopsychosocial factors (James, Keenan, Strogatz, Browning, & Garrett, 1992; McEwen, 2003b, 2008; McEwen & Stellar, 1993; Mullings, 2005; Sterling, 2004).

Homeostasis is an integrated, whole-body process of coping and adaptation to stress. Exposure to stressors does not automatically result in long term harmful effects. Homeostasis maintains of physiologic parameters in response to stressors that operate within a relatively narrow range of set-points (H. J. Cohen, 2000; Glei et al., 2007; Schulkin, 2003; Selye, 1983). Prolonged exposure to stressors or a an episode of acute stress precipitates sustained mobilization of physiologic stress responses, disruption of normal cellular and organ system function, and failure to restore homeostasis (McEwen, 2008; McEwen & Lasley, 2003). Chronic stress can be toxic due to the adverse effects of prolonged activation of neuroendocrine, inflammatory, cardiovascular, immune, metabolic, and coagulation systems (Geronimus, Hicken, Keene, & Bound, 2006; McEwen, 1993, 2008; McEwen & Lasley, 2003; Nielson, Seeman, & Hahn, 2007). Unremitting negative stress leads to sustained physiologic aberration in regulatory functions and failure of adaptive mechanisms that are critical in maintaining homeostasis. Chronic stress is a risk factor for morbidity, cognitive impairment, function decline, disability, and mortality (M. S. Clark, Bond, & Hecker, 2007; Geronimus, 2001; Geronimus et al., 2006; Glei, Goldman, Chuang, & Weinstein, 2007; McEwen, 1993,

2008; Newman et al., 2001). Chronic BPSS stress leads to physiologic wear-and-tear and compromised organ and system function, physiological dysregulation, and disease (Geronimus, 2001; Geronimus, Hicken, Keene, & Bound, 2006; Geronimus, Bound, Keene, & Hicken, 2007; Gruenewald et al., 2009). Chronic BPSS stress across the lifespan has been proposed as “catalysts of accelerated aging and agitators of disease trajectories” (Juster, McEwen, & Lupien, 2010, p. 2). The toxic effect of chronic stress is more prevalent in certain minority and high risk groups and may contribute to greater morbidity, mortality, and health disparities (M. S. Clark et al., 2007; Crimmins, Kim, & Seeman, 2009; Geronimus, 2001; Geronimus et al., 2006, 2007; McEwen, 1993, 2008; McEwen & Lasley, 2003; McEwen & Stellar, 1993; Szanton, Allen, Seplaki, Bandeen-Roche, & Fried, 2009; Whitson et al., 2011).

Acute and chronic cumulative stress is a pathogenic mechanism in disease and potentially in frailty through mechanisms related to prolonged dysregulation of biologic functions and proliferation of stress mediators that initiate inflammatory responses instrumental in development of disease and frailty. Stress theory strengthens the BPSS model by providing a theoretical and empirical base for the linkage between BPSS stressors, physiologic function, health, illness, and disease (McEwen, 1993, 2008; Puts et al., 2005; Sanders, Boudreau, Fried, Walston, Harris, & Newman, 2011; Seely & Christou, 2000; Stewart, 2006). The BPSS-Stress model, illustrated in Figure 1, offers a comprehensive framework for examining frailty.

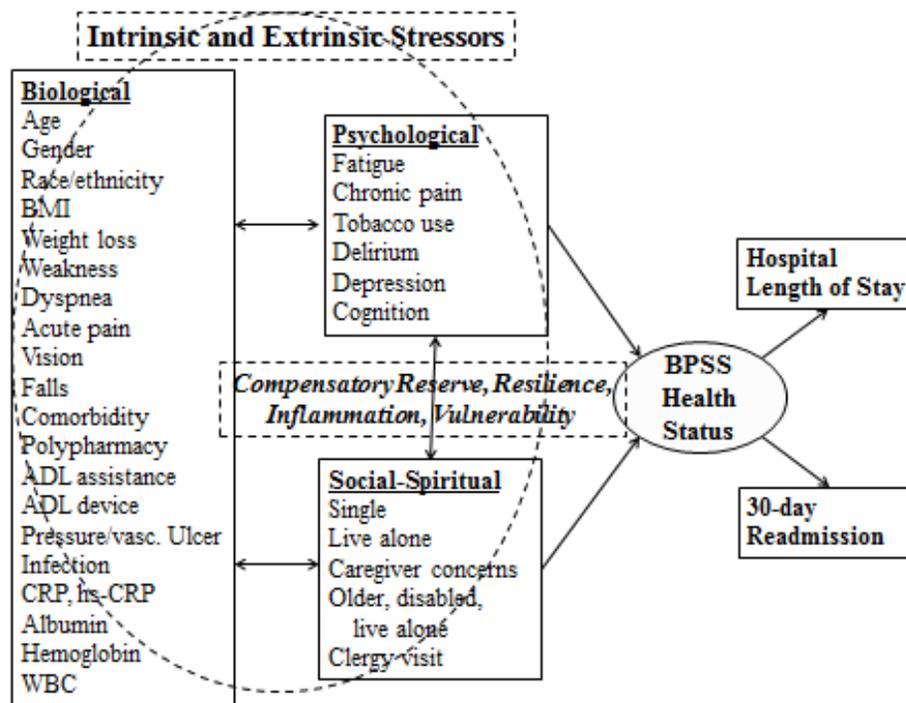


Figure 1. The Biologic-Psychologic-Social-Spiritual and Stress Model.

### Biologic Domain

The biologic domain refers to life-sustaining biologic and physiologic processes that enable human function. Healthy biologic function requires the seamless coordination of cells, tissues, organs and organ systems. Age-related changes in the neuroendocrine and immune systems contribute to abnormal levels of inflammatory, immunologic, and hormonal biomarkers and chronic low-grade inflammation (Ko, 2011; Phan et al., 2008; Yao et al., 2011; Walston & Fried, 1999; Walston et al., 2002). For example, acute phase reactant CRP which is produced and directly up-regulated by IL-6 is associated with increased risk for morbidity, sarcopenia, poor physical function, disability, and frailty (Cesari et al., 2004; H. J. Cohen et al., 2003; H. J. Cohen, Pieper, Harris, Rao, & Currie, 1997; De Martinis et al., 2006; Ershler & Keller, 2000; Ko, 2011; Leng et al., 2002;

Nielson et al., 2007; Okamura et al., 2008; Puts et al., 2005, 2005a; Walston et al., 2002). The combination of high CRP and low albumin level is associated with frailty (Harimurti & Setiati, 2007). Chronic elevation of the WBC count is associated with frailty (Leng, Hung, et al., 2009; Leng, Xue, et al., 2009). Hemoglobin and albumin are associated with inflammation, malnutrition, frailty, morbidity, and mortality even if abnormal levels can be explained by disease factors or nutritional deficiency (Arques, 2008; Don & Kaysen, 2004; Ko, 2011; Leng et al., 2002; Zakai et al., 2006). Inflammatory conditions such as rheumatoid arthritis, stroke, and cardiovascular disease are associated with frailty (S. S. Chang, Vaz Fragoso, Van Ness, Fried, & Tinetti, 2011; S. S. Chang et al., 2012; Phan et al., 2008; Silvestri et al., 2004). Other biomarkers have been studied in relation to frailty but it is unclear which biomarkers or clusters of biomarkers are most influential in its inception or progression (De Martinis et al., 2006; Ferrucci et al., 2002; Kanapura & Ershler, 2009; Ko, 2011) but biomarkers associated with inflammation are highly relevant since these types of biomarkers are also associated with chronic BPSS stress, chronic disease states including low grade infection (periodontitis, cytomegalovirus), and acute illness. Gender and race are biologic variables that are significantly associated with frailty, specifically, female gender and African American race (Hirsch et al., 2006; Puts et al., 2005a; Szanton et al., 2009; Yang & Lee, 2010).

Symptoms and conditions significantly associated with frailty are weakness, fatigue, dyspnea, pain, high and low BMI, obesity, cognitive impairment, depression, delirium, malnutrition, weight loss, pressure ulcers, visual impairment, and falls (Fried, Tangen, et al., 2001; Hackstaff, 2009; Hadley et al., 1993; Heuberger, 2011; Pel-Little et

al., 2009; Shega et al., 2012; Speechley & Tinetti, 1991; Xue, 2011; Xue, Bandeen-Roche, Varadhan, Zhou, & Fried, 2008). Symptoms are frequently related to different diseases. Comorbidity may be associated with symptom patterns that may provide a better understanding of overall morbidity status and function than comorbidity indexes alone (Whitson et al., 2009, 2011). Medication use impacts biologic function in positive and negative ways. Pharmacologic treatment of disease can improve health outcomes but medication side effects can introduce new risk.

### **Psychologic Domain**

The psychologic domain refers to cognitive, affective, intellectual, and behavioral processes that provide the human interface with physical and social environments. Measurement of psychologic function may be obtained by in-person interviews and interactions, self-report through completion of questionnaires, and via direct observation of behavior under naturalistic conditions or under conditions intended to provoke specific psychological or behavioral responses. Psychologic factors that are relevant to frailty are emotional health and coping, depression, anxiety, and attitudes and beliefs about health and illness that influence behaviors that are influential in the development of risk factors for frailty or are protective in the promotion of resilience.

### **Social Domain**

The social domain refers social networks, or the number and types of social contacts in a person's social circle, social integration, or the degree of connectedness and quality of relationships among social contacts and having a confidante, communicating and relating to others, having close personal ties and emotional connections with family,

friends, and the community (Loucks, Berkman, Gruenewald, & Seeman, 2006; T. E. Seeman, 1996; T. E. Seeman, Lusignolo, Albert, & Berkman, 2001). Social factors are influenced by cultural norms, beliefs, traditions, and practices. Social interaction and social support norms and preferences can differ markedly between cultural groups.

Social support may involve emotional support, companionship, illness-related care, informational support and problem-solving assistance, and instrumental support through provision of financial or material resources (Andrew, Mitnitski, & Rockwood, 2008; Nicklett et al., 2012; T. E. Seeman, 2000). Positive social support is related to good mental health and cognitive function (T. E. Seeman et al., 2001). Newsom and Schulz (1996) found that instrumental and emotional support alleviated the effects of disability on depressive symptoms and improved life satisfaction. In a concept analysis of support, Langford, Bowsher, Maloney, and Lillis (1997) found that the social network, embeddedness, and climate were antecedents of social support; consequences were personal competence, effective health maintenance and coping behaviors, perceived control, sense of stability, self-worth, and well-being, positive affect, and decreased anxiety and depression.

Cultural diversity is increasing in the U.S. Recent population data document that by 2050, racial and ethnic minority groups will continue to increase and Caucasians will be a minority group. Attention to cultural differences and the influence of culture on health and illness require understanding of cultural norms. Cultural norms and practices may differ by race and ethnicity based on geographic location, local family and community characteristics, socioeconomic status, education, religion, political

environment, and other factors. Within-group differences among racial and ethnic groups warrant attention when considering social support since assumptions about racial/ethnic groups cannot be assumed to generalize to the entire population. Cultural beliefs and racial and ethnic identity can influence health beliefs and healing practices, lifestyle behaviors, medical treatment adherence, caregiving patterns, and perspectives on dependence, interdependence, and independence in the context of aging and disease.

### **Spiritual Domain**

The spiritual domain includes the constructs of spirituality and religiosity. These terms been used interchangeably to describe ways in which people transcend their current experience or perception of self, relate to a spiritual entity or God, and enhance connectedness with others (Harvey & Silverman, 2007). Spiritual beliefs may be more salient than formal religious affiliation. Attitudes toward health may involve spiritual factors that help integrate physiologic, psychologic, emotional, social, and physical elements of disease or disability (Zittel et al., 2002). Spirituality and religiosity may have a positive effect on physical and mental health outcomes through different ways of ascribing meaning to health and illness (Harvey & Silverman, 2007; Koenig, George, & Titus, 2004; Levin, 1994; Levin, Taylor, & Chatters, 1994; Musick, 1996).

## **Research Questions**

### **Research Question 1**

What is the proportion of each of the 14 frailty components in hospitalized adults 55 years of age and older?

**Research Question 2**

What is the level of frailty in the sample of hospitalized adults, based on the Frailty Score (0–14)?

**Research Question 3**

What are the relationships between demographic, biological, psychological, and sociocultural health status variables and each of the 14 frailty components?

**Research Question 4**

What are the relationships between the demographic, biological, psychological, and social health status variables and level of frailty or the Frailty Score that ranged from 0–14?

**Research Question 5**

What is the relationship between level of frailty or the Frailty Score (range, 0 to 14) and length of hospital stay?

**Research Question 6**

What is the relationship between level of frailty or the Frailty Score (range, 0 to 14) and 30-day hospital readmission?

**Justification**

This study is needed in order to advance understanding of frailty in hospitalized adults because there is scant research on frailty in this population, especially in adults 55 years of age and older. Frailty is a formidable health care issue since it is associated with worse outcomes, longer length of stay, hospital readmissions, morbidity, and mortality. Empirical evidence for key components of frailty in hospitalized adults 55 years of age

and older is lacking therefore research is needed that extends the study of frailty from a biologic perspective to a comprehensive biopsychosocial perspective, and from adults 55 years of age and older who may be at risk for frailty or frail. There is little known about frailty and its assessment, primary and secondary prevention, and intervention to guide nursing practice in the hospital setting. Conceptual and operational criteria and defining characteristics for a frailty nursing diagnosis is needed but there is scant nursing research to guide this work. Nursing models for care for frailty are lacking. Strategies to enhance clinical nursing leadership at the bedside to facilitate interdisciplinary communication and collaboration to improve care of frail adults are also needed. A diversity of expertise ensures that patient and family needs and preferences are addressed by those most prepared to fully assess certain frailty issues.

### **Contributions of this Study**

This study expanded the study of frailty from older adults to include midlife adults 55 years of age and older, since evidence suggests that frailty and frailty risk factors and precursors are found well before the age of 65. Frailty was examined from a multidimensional BPSS perspective utilizing evidence-based frailty components derived from existing, readily available clinical data in the EMR to characterize frailty in hospitalized adults. A unique feature of this study was inclusion of four plasma biomarkers as frailty components that represent physiologic indicators that are significantly associated in prior research with inflammation, malnutrition, and frailty.

## Chapter Summary

Frailty is associated with chronic inflammation, multisystem physiologic dysregulation, biologic instability, and reduced compensatory reserve and ability to effectively respond to intrinsic and extrinsic stressors to maintain homeostasis (Abellan van Kan, Rolland, Morley, et al., 2008; Fried, Tangen, et al., 2001; Fullop et al., 2010; Zittel et al., 2002). Understanding frailty in hospitalized adults 55 years of age and older is important given lack of research in this vulnerable population and the deleterious outcomes. The multi-dimensional BPSS-Stress model was used to examine frailty in this study. The model aligns with nursing perspectives about health and illness, caring practices, and person-centered care.

The changing demographics of the U.S. population project greater longevity, increasing incidence and prevalence of chronic disease and obesity, and the limitations of existing knowledge about frailty is of considerable concern. Given the personal, societal, economic, and public health impact of frailty, it is vital that frailty not be ignored or interpreted as a terminal condition of old age with no hope for prevention or improvement (Fillit & Butler, 2009; Kanapura & Ershler, 2009; Palmore, 2004; Sarkisian & Lachs, 1996; Sarkisian, Gruenewald, Boscardin, & Seeman, 2008; T. E. Seeman, Merkin, Crimmins, & Karlamangla, 2010; Stone, Cafferata, & Sangl, 1987). Nursing research on frailty in hospitalized adults is limited thus there is little evidence to guide nursing practice (Mezey & Fulmer, 1998; Mitty, 2010). This study contributed to a body of literature that lacks substantive nursing research with the potential for advancing

understanding of frailty and elucidating implications for clinical practice, interprofessional collaboration, education, research, and public policy.

## **CHAPTER II**

### **REVIEW OF THE LITERATURE**

#### **Introduction**

Prior to the 1980s, frailty was an undefined term used to describe elderly who were very old, appeared feeble, thin, and fragile, had multiple chronic diseases, ADL limitations, disability, cognitive impairment, resided in a nursing home, or were near the end-of-life (Ahmed et al., 2007; Bergman et al., 2007; Heuberger, 2011; Karunanathan et al., 2009; Levers et al., 2006; Markle-Reid & Browne, 2003; Strawbridge et al., 1998). There was little recognition of frailty as a distinct clinical problem until the 1990s when demographic shifts demonstrated a steady increase in population longevity and higher rates of health care and social service resource utilization, particularly among the very old and frail elderly (Fries, 2005; Hackstaff, 2009; Mor, 2005; Izaks & Westendorp, 2003; Woo et al., 2006). Continued change in aging demographics and expected increases in morbidity and disability project that the incidence and prevalence of frailty and health care utilization and costs will also increase.

Around the 1970s, geriatric medicine became a subspecialty of internal medicine and family medicine that focused on prevention and treatment of diseases and disability in older adults. Similarly, gerontology emerged as a subspecialty in nursing and the social sciences where a focus on the biopsychosocial-spiritual dimensions of the aging process emerged (Burnside, 1990; Burnside & Touhy, 2006; Heuberger, 2011; Matteson &

McConnell, 1985). However, it was not until the 1990s when frailty gained increased attention from clinicians, researchers, and leaders in health care and public policy.

Increased longevity and total life expectancy increased at a rate that exceeded active life expectancy (Ferrucci et al., 2006; Katz et al., 1983). The notion that aging and frailty may be intrinsically connected and evolve in parallel drew attention to the need for better understanding about what mediates these two processes since living longer with more years of dependence and disability imposes significant burden on the individual and society with implications for health and social services, resource utilization, and public policy (Albert, Im, & Raveis, 2002; Ferrucci et al., 2006; Fries, 1980, 1988; Jeune, 2002).

Interdisciplinary conferences, international symposiums, and expert panels advanced theoretical perspectives, launched research, and began to characterize frailty and consider the clinical practice implications of the growing number of older adults, especially frail elderly (Abellan van Kan, Rolland, Morley, et al., 2008; Hadley et al., 1993; Hogan, MacKnight, & Bergman, 2003; Katz et al., 1983; Raphael et al., 1995; Rodríguez-Mañas et al., 2012; Vellas et al., 2012; Walston et al., 2006). Frailty emerged as an important area of research that focused on how to define frailty and provide care to this vulnerable population (Abellan van Kan, Rolland, Bergman, et al., 2008; Ferrucci et al., 2006; Gealey, 1997; Vellas et al., 2012; Fried, Herdman, Kuhn, Rubin, & Turano, 1991; Fries, 1988). Despite an increasing body of science, frailty remains poorly understood from pathophysiologic and biopsychosocial perspectives with limited consensus on a theoretical or operational definition of frailty that is applicable across settings and populations (Abellan van Kan, Rolland, Bergman et al., 2008; Fried et al.,

2005; Gobbens et al., 2010, 2010a, 2010c; Karunanathan et al., 2009; Kuh, 2007; Levers et al., 2006; Markle-Reid & Browne, 2003; Mohandas, Reifsnnyder, Jacobs, & Fox, 2011; Rockwood, 2005; Rodríguez-Mañas et al., 2012).

Significant gaps persist in understanding the biopsychosocial and physiologic and genetic underpinnings of frailty and its precursors, risk factors, defining characteristics, clinical indicators, and diagnostic criteria (Bortz, 2002, 2008; Ferrucci, Mahallati, & Simonsick, 2006; Rodríguez-Mañas et al., 2013; Sternberg, Wershof Schwartz, Karunanathan, Bergman, & Mark Clarfield, 2011; Xue, 2011). Most frailty research has been conducted in medically-stable community-living older adults with a primary focus on biologic frailty. Little is known about the natural history and early manifestations of frailty in younger adults and the psychosocial, cultural, and historical factors that link aging and frailty as related constructs (Ferrucci et al., 2004, 2006; Fried et al., 2005; Karunanathan et al., 2009; Levers et al., 2006; National Institute on Aging, 1991; Pel-Little et al., 2009; Rodríguez-Mañas et al., 2012). Of considerable importance is the lack of research on frailty in acutely ill hospitalized adults, a group that may be uniquely at high risk due to the interactive and dynamic effects of acute illness, trauma, surgery, medications, procedures, treatments, immobility, pain and sleep disturbances, and a myriad of other factors.

Defining frailty is challenging since there is insufficient evidence for an accurate description of its etiology, clinical indicators, or typology that captures the complexity of this condition (Ahmed et al., 2007; Bergman et al., 2007; Gobbens et al., 2010, 2010a; Fried et al., 2009; Hogan, 2006; Xue, 2011). Frailty presentation varies widely in its

onset and its clinical manifestations (Sternberg et al., 2011; Xue et al., 2008). Frailty is generally characterized as a progressive biologic process of decline due to impaired physiologic function across multiple body systems resulting in reduced compensatory reserve, poor resilience, and lower response to and recovery from intrinsic and extrinsic stressors (Ahmed et al., 2007; Bergman et al., 2007; Bortz, 1993, 2008, 2010; Yassuda et al., 2012). It is unclear if frailty is a natural consequence of aging and disease, a product of interactions between aging processes, disease conditions, and biopsychosocial and environmental factors, or if frailty is a unique condition independent of these factors (Bergman et al., 2007; Bortz, 2002; Fulop et al., 2010; Izaks & Westendorp, 2003; Morley et al., 2006). There is substantial evidence that cumulative stress and activation of inflammatory and coagulation pathways are significant factors that create differential risk for frailty and its clinical presentation (Barzilay et al., 2007; De Martinis et al., 2006; Heuberger, 2011; National Institute on Aging [NIA], 2004; Schmaltz et al., 2005; Walston et al., 2002; Yao, Li, & Leng, 2011). Chronic inflammation is associated with detrimental physiologic changes that progressively lead to biologic vulnerability and frailty (S. S. Chang et al., 2012; Franceschi et al., 2000; Ho et al., 2011; Kanapuru & Ershler, 2009; Puts et al., 2005; Walston et al., 2002; Yao et al., 2011).

Clinical features of frailty are vague and ambiguous. The literature is replete with commentary that clinicians recognize frailty based on personal experience and subjective appraisal that associates frailty with advanced age, changes in physical appearance and behavior, and other manifestations (Fried et al., 2004; Studenski, et al., 2004). Signs and symptoms may include muscle weakness, fatigue, low physical activity, poor endurance,

impaired physical function, low body weight, poor appetite, unplanned weight loss, cognitive impairment, depressive symptoms, and decreased social interaction (Ahmed et al., 2007; Fried et al., 2005; Gobbens et al., 2010a; Hubbard, O'Mahony, & Woodhouse, 2008; Lally & Crome, 2007; Mitnitski, Fallah, Rockwood, & Rockwood, 2011; Morley, 2010; Morley et al., 2006; Rodríguez-Mañas et al., 2012; Walston et al., 2006; Xue, 2011; Yao et al., 2011). No single sign or symptom, cluster of signs and symptoms, or physiologic measures definitively characterized frailty. Indeed, frailty is not always visibly detectable and may only be discovered after an acute health threat where health status outcomes and recovery is far worse than would be expected in persons in similar circumstances (Slaets, 2006). Frailty has been described as a precarious state of health with greater susceptibility for negative outcomes from minor illness or trauma. Non-life-threatening events such as acute urinary tract or pulmonary infection destabilizes homeostasis and unleashes a cascade of aberrant physiologic processes that result in a series of adverse consequences that negatively impacts health status and function (Fried et al., 2009; Puts, Lips, & Deeg, 2005b; Romero-Ortuno, Walsh, Lawlor, & Kenny, 2010; Sarkisian et al., 2008; Sourial et al., 2010; Xue, 2011 ).

In early phases of frailty, minor declines in physiologic function evolve and progress at different rates across multiple organ systems with little objective evidence of diminishing physiologic reserve or impaired function. Thus, frailty may be undetected when intrinsic and extrinsic stressors do not exceed biopsychosocial adaptive and compensatory responses that maintain homeostasis. However, when intrinsic or extrinsic stressors are of sufficient magnitude to overcome marginal physiologic reserves,

compensatory biologic processes are inadequate and fail to effectively respond to stressors and a downward trajectory of decline in physiologic function ensues (Ahmed et al., 2007; De Lepeleire, Iliffe, Mann, & Degryse, 2009). Frailty is not a static condition, nor is its course predictable, inevitably progressive, or irreversible. Data from longitudinal cohort studies characterize frailty as a state of stable-instability with dynamic interactive physiologic processes, fluctuating levels of vulnerability, and shifts between levels of frailty (Gill et al., 2006; Puts et al., 2005b). Thus, identifying frailty is challenging with profound implications for clinical decision-making regarding medical, surgical, procedural, and pharmacologic intervention in the management of acute illness, trauma, and chronic disease in hospitalized adults.

Frailty has been proposed as a better predictor of compromised organ system function and risk for disease and poor outcomes than chronological age and sociodemographic indicators (De Lepeleire et al., 2009; Sanders et al., 2011). The heterogeneity in health status and function noted in older adults of similar ages is partly explained by the different ways in which people age. Individual differences in biology, genetics, disease conditions, lifestyle behaviors, access to health care, living circumstances, the physical and social environment, and other factors dynamically interact across the lifespan leading to considerable variability among individuals in aging processes, health status, and disease. Given this, it is not surprising that what instigates frailty remains unclear since no single etiology or group of etiologies can explain how or why frailty develops in aging adults represented by such diversity.

Frailty is of concern at the individual and societal level because it is associated with a myriad of negative outcomes including morbidity, functional decline, disability, hospitalization, prolonged or poor recovery, institutionalization, and mortality (Fried, Tangen, et al., 2001; Fried et al., 2004; Fugate Woods et al., 2005; Heppenstall, Hanger, & Wilkinson, 2009; Karunanathan et al., 2009; Levers et al., 2006; Raphael et al., 1995). Hospitalization poses a threat to frailty trajectories with increased risk for functional decline, new dependence, disability during and after hospitalization and nursing home discharge (T. M. Gill, Allore, et al., 2010; Gill et al., 2009; Gill, Gabhauer, Han, & Allore, 2010; Gill et al., 2011; Heppenstall et al., 2009). Of considerable importance is evidence that frailty is potentially reversible or its progression halted or delayed. Interventions that address risk factors, symptoms, and disease management can lead to significant gains in health status and function (Gill et al., 2006; Mitniski et al., 2011; Mitnitski, Song, & Rockwood, 2007; Puts et al., 2005b; Rockwood et al., 2011).

Frailty is a compelling national and global public health issue that significantly impacts individuals, families, communities, and society. Because of the magnitude of the impact of frailty on an aging population and all sectors of society, the IOM has identified frailty as a priority for improvement in health care quality (Adams & Corrigan, 2003). The future needs of the growing aging population has drawn attention to a health care delivery system that is poorly prepared to help aging adults, especially those who are medically complex and frail. Existing health care delivery models are primarily oriented towards specialty practice that is disease- and organ-system focused. As a result, care delivery is often fragmented, and patient education can be confusing and conflicting.

According to the IOM, the current health care system has failed to have a significant impact on health outcomes, readmission rates, and costs despite many health care innovations (De Lepeleire et al., 2009; IOM, 2008; CMS, 2012a). Given demographic trends and changing family structures, there will be greater need for a wider range of services that promote effective transitions in care and resources that enable independent living and other supportive living arrangements. Thus, frailty assessment, primary and secondary prevention, and targeted intervention will be crucial in clinical practice. The anticipated increase in the incidence and prevalence of frailty and its adverse consequences underscores the need to better understand frailty especially in hospitalized adults since there is insufficient research to guide practice.

### **Conceptual Model**

The conceptual model for this study is based on the biologic, psychologic, social, spiritual model and stress theory (BPSS-Stress model). This model was appropriate for the study because frailty is a multidimensional, multifaceted condition that affects all aspects of human function through complex nonlinear interactions within the individual and between the individual and the external social and physical environment. Stress theory is an important part of the conceptual model because there is strong evidence that chronic stress directly and indirectly affects the BPSS domains and function (Logan & Barksdale, 2008; McEwen, 1993, 2008; McEwen & Stellar, 1993; McEwen & Wingfield, 2010; Nielson, Seeman, & Hahn, 2007; Schulkin, 2003; T. E. Seeman, 2000; T. Seeman, Dubin, & Seeman, 2003). Chronic stress incites physiologic processes that adversely impact BPSS function and increases risk for acute illness, chronic disease, disability, and

frailty (Logan & Barksdale, 2008; McEwen, 1993, 2008; McEwen & Wingfield, 2010; Szanton et al., 2005).

### **Stress Theory**

Stress is a common human experience. Stress refers to the human response manifested through physical and emotional stimulus that disrupts equilibrium, causing mental or emotional strain or worry. Stress arises from psychological, social, biological, and environmental stimuli that incite various degrees of physiological stress responses (Selye, 1955, 1974). Physiologic responses are mediated by a person's perception and interpretation of the stressor as benign, an annoyance, or a threat. The stress response is highly individualized and contextual (Lazarus & Folkman, 1984). While some stress is necessary for normal function, prolonged stress perceived as negative adversely affects health (E. D. Carlson & Chamberlain, 2005; Geronimus, 2001; James et al., 1992; McEwen, 1993, 2008; McEwen & Stellar, 1993; Mullings, 2005). A person's cognitive appraisal of stressful events, life circumstances, and stress burden influences physiologic stress responses (Lazarus & Folkman, 1984). According to Lazarus and Folkman (1984), stress involves three processes. Primary appraisal is the cognitive process of perceiving a threat to oneself, secondary appraisal is the process of conceiving of potential responses to the threat, and coping is the process that involves taking action in response to the perceived threat. These processes are nonlinear and interactive with one's emotional state. Further, the outcome of a coping response may lead to other stressors and emotional reactions. Lazars and Folkman's work focused primarily on chronic stress and

its adverse effects, whereas in comparison, Selye used the term *distress* for negative stress and *eustress* for positive stress.

Perception of a stressor as negative activates behavioral and physiologic stress responses that instigate biologic processes that contribute to development of illness and disease (Goldman, Gleib, Seplaki, Liu, & Weinstein, 2005; Schulz & Williamson, 1993). Although the term stress was not widely recognized by nurse researchers until the 1970s, references to stress began appearing in nursing journals in the 1950s. Anecdotal reports from patients and empirical evidence from researchers in nursing and other disciplines indicated that stress and health were inextricably related concepts.

Chronic stress is particularly damaging because it results in a prolonged state of hyper-vigilance, anxiety, and worry that can lead to significant biologic dysregulation. Chronic stress activates physiologic responses in multiple inter-related organ systems and produces significant abnormal changes in neuroendocrine, cardiovascular, hematologic, metabolic, and immunologic function. Chronic stressors have been described as a “catalysts of accelerated aging and agitators of disease trajectories” (Juster et al., 2010, p. 2). Chronic stress and poor cognitive and biologic adaptation responses lead to disease risk factors and eventually to disease (E. D. Carlson & Chamberlain, 2005; Clark, Anderson, Clark, & Williams, 1999; Clark et al., 2007; Gleib et al., 2007; Juster et al., 2010; Logan & Barksdale, 2008; McEwen, 1993, 2003b, 2008; Stewart, 2006).

Research suggests that stressors and adverse conditions during childhood and throughout the lifespan produce variations in health status and risk for poor health outcomes within and across groups (Clark et al., 1999; Jung, Gruenewald, Seeman, &

Sarkisian, 2010; Kuh, 2007; T. E. Seeman, 1996; T. E. Seeman & Crimmons, 2001; T. E. Seeman & McEwen, 1996). Socioeconomic stressors (poverty, poor living conditions, financial hardship, workplace pressure, family conflict, low education) are potent sources of stress that confer biological risk that may accelerate aging and the early onset of disease, disability, and frailty (Crimmons et al., 2009; Geronimus et al., 2006; Gill & Szanton, 2011; Gregory et al., 2011; Guralnik, Land, Blazer, Fillenbaum, & Branch, 1993; Szanton et al., 2008; Szanton, Seplaki, et al., 2010).

**Inflammation.** Stress is associated with inflammation. The aging immune system manifests as a state of low-grade, chronic, systemic inflammation (Franceschi et al., 2000; Xue, 2011). Age-related chronic inflammation, or inflamm-ageing, is hypothesized to be the underlying pathogenesis of tissue damage and organ dysfunction (De Martinis et al., 2006; Franceschi et al., 2000). Systemic inflammation progressively causes cellular and organ system dysregulation and directly contributes to functional decline, disability, and morbidity (Bandeem-Roche, Walston, Huang, Semba, & Ferrucci, 2009; Kanapuru & Ershler, 2009; Xue, 2011). Cumulative stress stimulates complex responses in the sympathetic and parasympathetic nervous systems and the hypothalamus-pituitary-adrenal axis (HPA) which activates neuroendocrine, cardiovascular, hematologic, immune, and metabolic systems (McEwen, 1993; Sterling, 2004). Under normal conditions, these systems dynamically interact in complex ways to facilitate homeostasis. Homeostasis represents the coordination of a wide range of biologic processes that operate within relatively narrow parameters to sustain normal biologic function (e.g., core body temperature, hydration). Homeostasis fails when stressors (e.g., infection,

dehydration, hypoxia) induce physiologic conditions that exceed adaptive parameters. Biologic efforts that mobilize corrective responses are ineffective, resulting in life-threatening situations (e.g., hyperthermia, hypernatremia, cardiac arrhythmias, seizures).

Chronic, low-grade inflammation may be a consequence of lifelong exposure to the cumulative effects of stress and negative physiologic stress responses, genetics, increased antigenic load, chronic disease, and lifestyle behaviors (De Martinis et al., 2006; Franceschi et al., 2000). Chronic low-grade systemic inflammation is a significant contributor in the pathogenesis of medical conditions associated with frailty including atherosclerosis, hypertension, cardiovascular disease, myocardial infarction, stroke, cancer, depression, osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, Alzheimer's disease, Parkinson's disease, coagulation disorders, chronic infection, HIV/Aids, post-traumatic stress disorder, and Crohn's disease (Ahmed, Sherman, & Vanwyck, 2008; Cacciatore et al., 2005; Cesari et al., 2003a, 2003b; De Martinis et al., 2006; Don & Kaysen, 2004; Ishihara-Paul et al., 2008; Kanapuru & Ershler, 2009; Kiss & Szodoray, 2010; Koelewijn, Schwartz, Samsom, Oldenburg, 2008; Leng et al., 2002; Linares, Gomez-Reino, Carreira, Morillas, & Ibero, 1986; Mohile et al., 2009; Nielson, Seeman, & Hahn, 2007; Phan et al., 2008; Puts et al., 2005).

Chronic inflammation is independently associated with frailty without comorbidity (Ferrucci et al., 2002; Kanapuru & Ershler, 2009; Leng et al., 2007; Puts et al., 2005; von Känel, 2006; Walston et al., 2002; Williams, Harmon, Burlingame, & Du Clos, 2005; Xue, 2011). Inflammatory biomarkers such as abnormal levels of serum IL-6, CRP and hs-CRP, albumin, hemoglobin, and WBC count are associated with poor

physical function, disability, mortality, and frailty (Bautmans, Njemini, Lambert, Demanet, & Mets, 2005; De Martinis et al., 2006; Ferrucci et al., 2002; Ishihara-Paul et al., 2008; Leng et al., 2002; Newman et al., 2001; Puts et al., 2005; Steptoe et al., 2007; Walston et al., 2002; Xue, 2011).

In the MacArthur Studies of Successful Aging of healthy community adults ( $N = 870$ , 70–79 years), serum albumin, cholesterol, IL-6, and CRP were analyzed as a composite measure of inflammation (Reuben, Judd-Hamilton, Harris, & Seeman, 2003). For each biomarker, one point was allotted for laboratory values that were above or below established parameters. A composite sum for inflammation was computed to determine risk for mortality and functional decline. Mortality at three and seven years was 6% and 23%, respectively. Those with 1 or 2 biomarkers were at moderate risk for mortality at each time point (adjusted  $OR = 1.5$  and  $1.3$ , respectively, not statistically significant). Those with three or four biomarkers had statistically significantly higher mortality risk (adjusted  $OR = 6.6$  and  $3.2$ , respectively) compared to those who had none.

Abnormal inflammatory biomarkers are associated with psychosocial stressors such as low socioeconomic status (SES), work stress, early life adversity, hostility, and social isolation (Alley et al., 2006; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Kiecolt-Glaser et al., 2005; Koster et al., 2006; Steptoe et al., 2007; Ranjit, Diez-Roux, Shea, Cushman, Ni, et al., 2007; Ranjit, Diez-Roux, Shea, Cushman, Seeman, et al., 2007). Stress-related lifestyle factors associated with frailty are physical inactivity, poor nutrition, smoking, excessive alcohol use, and obesity (Hackstaff, 2009; Hadley et al., 1993; Rapuri, Gallagher, & Smith, 2007; Reuben et al., 2003). Sustained abnormal levels

of inflammatory biomarkers provide a physiologic imprint of chronic stress that manifests as the loss of adaptive processes that ultimately exerts deleterious consequences on health status and increases risk for frailty (Gruenewald et al., 2009; Logan & Barksdale, 2008; McEwen, 1993, 2008).

### **Homeostasis, Allostasis, and Allostatic Load**

The concept of allostasis was introduced in 1988 by Sterling and Eyer to describe a process that operates in tandem with homeostasis to maintain normal ranges for physiologic parameters. Unlike homeostasis which operates within narrow ranges for set points to maintain physiologic parameters for body temperature, pH and hydration status, allostasis activates adaptive responses that have a wider range of physiologic parameters that involve many complex, nonlinear, inter-related systems and chemical mediators. Homeostasis and allostasis are both dynamic endogenous physiologic systems that together maintain the internal stability of an organism (Glei et al., 2007; McEwen, 1993, 2008; Sterling, 2004; Stewart, 2006).

Homeostasis derives from the Greek term, *homeo*, which means similar, while *stasis* means stand. In contrast to perspectives of homeostasis as a static state of physiologic stability, homeostasis is a physiologically dynamic state. Allostasis derives from the Greek term, *allo*, which means variable. Allostasis refers to biologic functions that maintain stability through change (Sterling, 2004). Allostasis facilitates rapid physiologic responses that results in elevated blood pressure, pulse, and respiratory rate, diaphoresis, cognitive alertness, and neuromusculoskeletal reactivity. When the stressor abates, allostasis facilitates normalization of biochemical mediators and normal

physiologic function gradually resumes (Karlamañgla, Singer, McEwen, Rowe, & Seeman, 2002; Logan & Barksdale, 2008; McEwen, 2008; Nicolson, Storms, Ponds, & Sulon, 1997; Nicolson & van Diest, 2000).

Multiple physiologic systems and their biochemical mediators are activated in the stress response, including the hypothalamus-pituitary-adrenal (HPA) axis (cortisol, epinephrine, norepinephrine), immune system (IL-6, CRP, TNF- $\alpha$ ), and hematologic and metabolic system (fibrinogen, d-dimer, insulin-like growth factor). These mediators of the stress response have both protective and damaging effects on the body. In the short run, they are essential for adaptation, homeostasis, and survival. Repeated exposure to stressors or sustained cumulative stress leads to persistent activation of allostasis processes. Persistent over-activation of the stress response and sustained allostasis leads to significant physiologic dysregulation, poor adaptation and recovery, and failure of allostasis to normalize physiologic processes.

Sustained dysregulation adversely affects multiple organ systems and is described as allostatic load (McEwen, 2003a; McEwen & Lasley, 2003; McEwen & Wingfield, 2010; Stewart, 2006). The aberrant physiologic responses that lead to allostatic load are described as follows: (a) repeated, frequent exposure to multiple stressors; (b) failure of body systems to habituate to repeated exposure to the same stressors; (c) failure to down-regulate and turn-off the body's response to stressors in a timely manner; and (d) inadequate response by biochemical mediators to stressors that lead to compensatory hyperactivity of other mediators (McEwen, 2003a, 2008; Sterling, 2004; Stewart, 2006). Allostatic load eventually leads to changes in cellular and organ function and ultimately,

progressive decline across multiple organ systems and finally, end-organ damage (Glei et al., 2007; Karlamangla et al., 2002; Logan & Barksdale, 2008; McEwen, 1993, 2008; McEwen & Stellar, 1993; Szanton et al., 2009). Sustained activation of the stress response and allostatic load have profound detrimental health effects including increased risk for disease and disabling symptoms, impaired physical and cognitive performance, disability, and frailty (Bandeem-Roche et al., 2006; Goldman et al., 2005; Gruenewald et al., 2009; Hogan et al., 2003; Juster et al., 2010; Kumari et al., 2009; McEwen, 2008; McEwen & Lasley, 2003; Nielson et al., 2007; Stewart, 2006).

High allostatic load is toxic. Allostatic load is associated with cardiovascular disease and atherosclerosis (Logan & Barksdale, 2008; McEwen, 2008; Newman et al., 2001; Szanton et al., 2005), early onset of disease, disability, and mortality (Geronimus et al., 2006; Reuben et al., 2002; T. E. Seeman, Singer, Rowe, Horwitz, & McEwen, 1997), functional decline (Karlamangla et al., 2002), cognitive impairment (Wikby et al., 2005), mood disorders (McEwen, 2003b), chronic fatigue syndrome (Maloney, Boneva, Nater, & Reeves, 2009), post-traumatic stress disorder (Gill & Szanton, 2011), cancer (Retornaz et al., 2008), HIV/AIDS (Kuller et al., 2008; Terzian et al., 2009), and frailty (Gruenewald et al., 2009; Szanton et al., 2009; Toye et al., 2006).

In a longitudinal study of high-functioning older adults 70 to 79 years of age, the association between 13 biomarkers included in an index for allostatic load and frailty was examined (Gruenewald et al., 2009). In multivariable modeling adjusted for sociodemographic, health, and behavioral factors, a one-unit increase in the allostatic load score at baseline was associated with a 10% greater likelihood of frailty at three-year

follow-up (cumulative  $AOR=1.10$ ; 95%  $CI = 1.03-1.19$ ) (Gruenewald et al., 2009, p. 1525). No single biomarker independently predicted frailty. Multisystem physiological dysregulation was associated with greater risk of frailty. It was unclear if certain biomarkers or combinations of biomarkers are predictive of frailty. Evidence of significant relationships between chronic stress, dysregulated physiologic stress responses and poor adaptive stress responses, low-grade chronic inflammation, allostatic load and high risk for frailty warrants further research.

### **Demographic Data**

Demographic data include the deidentified patient identification number for the study, preadmission location, and admitting service (general medicine, cardiology, orthopedics), hospital length of stay, and 30-day hospital readmission.

### **Biologic Domain**

**Age.** Age is defined as the accumulation of damage to cells leading to incremental organ dysfunction and loss of biologic system redundancies, complexity and physiologic adaptability under stress (Izaks & Westendorp, 2003). Fedarko (2011) defines aging as deterioration of functional properties of cells, tissues and organs that gradually diminishes homeostasis and adaptability to internal and external stressors. The World Health Organization divides old age into three groups: young-old (60–74 years), old-old (75–84 years), and oldest-old (over 85 years). Centenarians are over 100 years of age and middle-aged adults are between 45 and 65 years of age.

The aging process, independent of disease, is characterized by progressive decline in cellular and organ mass and function that progresses at different rates over

time, but do not fall below a threshold that permits normal life (Bortz, 1993, 2008; Ferrucci et al., 2002). Aging changes evolve as the interplay of intrinsic and extrinsic factors unique to the individual and manifests in a “mosaic” progression (Fulop et al., 2010, p. 549). Aging is associated with complex nonlinear changes in physiologic and reduced and inefficient compensatory reserve and resilience, described as homeostenosis (Bortz, 2008; Fried et al., 2009; Lipsitz, 2004; Lipsitz & Goldberger, 1992; Shega et al., 2012). Surprisingly, most aging organ systems retain considerable function despite substantial loss of cellular function. Up to 70% of organ function can be compromised or lost before clinically significant failure occurs (Bortz, 2002).

Research suggests that chronological and biologic age are different paradigms for evaluating health status since they are poorly correlated until around 85 to 90 years of age when the cumulative effects of normal aging processes, chronic disease, lifestyle habits, and functional impairments become more intricately linked (Bortz, 2010; Fedarko, 2011; Woodhouse & O’Mahony, 1997). Aging is not an autonomous process unaffected by internal and external biopsychosocial factors and stressors (Bortz, 2002; Fillit & Butler, 2009; Fulop et al., 2010). Chronological age may be useful in assessing physical performance and organ systems function but is of limited value in those who are medically and functionally complex. The biologic complexity of aging and cumulative effect of comorbidity is more accurate and relevant in assessment (Yang & Lee, 2010). Biologic age provides a better estimation of health status than chronologic age, especially among those who experience accelerated aging where health status is worse than

expected for stated years (Crimmins et al., 2009; Federal Interagency Forum on Aging-Related Statistics, 2010; Lally & Crome, 2007; Montesanto et al., 2010).

Although frailty is associated with the aging process since its incidence and prevalence increases over time, underlying physiologic mechanisms are not entirely related to chronology (Afilalo et al., 2009). Frailty follows a physiologic pathway separate from aging and disability) and may represent an intermediate state between successful aging and pathological processes (Bortz, 2002; Purser et al., 2006; Whitson et al., 2007).

**Gender.** Research indicates that women have higher incident and prevalent frailty compared to men (Fernandez-Bolaños et al., 2008; Fried, Tangen, et al., 2001; Jones et al., 2005; Peterson et al., 2009; Puts et al., 2005a; Walston & Fried, 1999). In the Cardiovascular Health Study, 7.3% of women were frail compared to 4.9% of men. Research indicates that frail men experience earlier mortality but frail women live longer and have greater morbidity and disability (Puts et al., 2005a). Gender differences in anatomic structure (e.g., muscle mass and quality), hormonal influences, lifestyle behaviors, occupation, social roles, living circumstances, and exposure to stressors and stress responses may contribute to physiologic changes and differential risk for frailty (Fernandez-Bolaños et al., 2008; Ferrucci et al., 2004; Puts et al., 2005a).

In a study static and dynamic frailty in older adults ( $N = 2,257$ ), more women than men were frail in both the static and dynamic trajectory (10% and 6.9%, respectively) but the prevalence of static frailty was higher in women than men (18% versus 14%) and the prevalence of dynamic frailty was similar in both men and women (17% and 18%,

respectively; Puts et al., 2005b). Among women, weight loss, reduced peak flow, cognitive decline, vision loss, depressive symptoms, and low physical activity were associated with mortality. In men, only weight loss and depressive symptoms were associated with mortality. Despite differences in frailty risk factors, mortality was higher in frail men (50%) compared to women (27%) and nonfrail men (15%) compared to women (7%), independent of chronic disease and disability.

A biologic model for frailty may explain the higher prevalence rates of frailty in women compared to men based on gender differences related to sarcopenia, hormonal and neuroendocrine decline, and immune dysfunction (Walston & Fried, 1999). Men have higher baseline levels of muscle mass that may protect against the rapid muscle loss and strength associated with sarcopenia. Neuroendocrine and hormonal factors such as higher levels of testosterone and growth hormone may preserve muscle mass longer in men. Changes in the immune system increases risk for infection in men and chronic inflammatory conditions and muscle mass loss in women. Among women, certain biological, social and behavioral factors may contribute to greater longevity as well as factors that result in a greater frailty burden (Rockwood & Hubbard, 2004). Reduced longevity in men is associated with lower physiological reserve at older ages and health deficits that are more lethal. In contrast, women require high levels of energy and nutritional reserves related to childbearing, and if exhausted, may later experience poorer physiologic reserve (Rockwood & Hubbard, 2004). Gender differences in frailty incidence and prevalence may also be related to lifestyle behaviors such as physical

activity and exercise that is of lower frequency, intensity, and duration, and less high quality nutrient intake which is more common in women (Walston & Fried, 1999).

**Race/Ethnicity.** Research documents the highest prevalence of frailty among African Americans (Afilalo et al., 2009; Bergman et al., 2007; Cigolle, Ofstedal, Tian, & Blaum, 2009; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Hirsch et al., 2006; Whitson et al., 2011). In the Cardiovascular Health Study ( $N = 5,277$ ,  $\geq 65$  years, 15% African American) African American race was an independent predictor of frailty and African American women had the highest rate of frailty (Hirsch et al., 2006). Fifteen percent of African American women were frail compared to 6.8% of White women, 4.6% of White men and 8.7% of African American men. In adjusted models, non-obese African Americans had four-fold greater odds of frailty compared to Whites. In the Health and Retirement Study ( $N = 11,113$ ,  $\geq 65$  years, community and nursing home) African American women were more likely to be frail than White women (Cigolle et al., 2009). In the Women's Health Initiative–Observational Study ( $N = 40,657$ , 6.5% African American), African American women were significantly more likely to be frail (28%) than White women (15%), and more White women (57%) than African American women (38%) were nonfrail (Fugate Woods et al., 2005).

In a cross-sectional analysis of the Women's Health and Aging Studies ( $N = 727$  women  $\geq 65$  years) relationships between race, SES measures (education, income), and frailty were examined (Szanton, Seplaki, et al., 2010). In adjusted models, older women with low education had three times the odds of frailty compared with more educated women. Women with an annual income  $< \$10,000$  had two times the odds of frailty

compared to those with higher income, independent of age, race, health insurance status, comorbidity, and smoking. African Americans were significantly more likely to be frail than Caucasians but not after adjusting for education. An important consideration is that African American women experience earlier onset and accelerated progression of disease and disability compared to White women thus higher rates of frailty in this population is of concern (Geronimus, 2001; Hirsch et al., 2006; Whitson, Landerman, et al., 2010).

Research suggests that African Americans experience high levels of stress that are associated with negative health outcomes and frailty (Hirsch et al., 2006; Szanton, Thorpe, & Whitfield, 2010; Szanton et al., 2008). Key stressors are susceptibility to poor health and mental health problems, job discrimination, poor housing, low education, financial pressures, low access to and utilization of health and social services, and chronic exposure to racism and sexism (Clark, 2001; Clark et al., 2007; James et al., 1992; Mullings, 2005; Phillipson, 2002; Szanton, Seplaki, et al., 2010). Research indicates that perceived racism is a source of stress that influence early onset and severity of disease, greater symptom burden, disability, and has a deleterious impact on mental health and well-being (Clark, 2001; Clark et al., 1999; Crimmins et al., 2009; Geronimus, 2001; James et al., 199; Mullings, 2005; Weber & Fore, 2007).

**Body mass index.** Body mass index (BMI) is defined by World Health Organization (WHO) criteria (WHO, 2006) as weight in kilograms divided by square of height in meters ( $\text{kg}/\text{m}^2$ ). BMI classifies underweight, normal weight, overweight and obesity in adults using the following metrics: Severe thinness ( $< 16 \text{ kg}/\text{m}^2$ ), Underweight ( $< 18.5 \text{ kg}/\text{m}^2$ ); Normal ( $18.5\text{-}24.9 \text{ kg}/\text{m}^2$ ), Overweight ( $> 25 \text{ kg}/\text{m}^2$ ), Preobesity ( $25\text{-}29.9$

kg/m<sup>2</sup>); Obesity (> 30 kg/m<sup>2</sup>), and Obese Class I (30-34.9 kg/m<sup>2</sup>), Obese Class II (35-39.9 kg/m<sup>2</sup>), and Obese Class III ( $\geq$  40 kg/m<sup>2</sup>) (WHO, 2006). BMI values are not differentiated by age or sex therefore different body proportions, bone structure, and degree and location of adiposity should be considered. Abdominal adiposity, not reflected in BMI, is significantly associated with increased levels of inflammatory biomarkers and risk for disease. Recent unplanned weight loss and either low and high BMI are predictors of frailty (Ávila-Funes et al., 2009; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Rothman et al., 2008; Sarkisian et al., 2008; Xue et al., 2008). Weight loss not due to exercise or diet may be the result of disease processes or chronic stressors that exert catabolic effects via increased inflammatory neuroendocrine activation, processes that alter glucose metabolism, medications that decrease appetite, higher energy expenditure that exceeds nutritional intake, and socioeconomic factors that limit access to high quality nutrients (Bartali et al., 2006; Walston et al., 2006; Yao et al., 2011). In healthy older adults biomarkers associated with inflammation and malnutrition were associated with shorter lifespan (Carrière, Dupuy, Lacroux, Cristol, & Delcourt, 2008).

Although most frailty research cites low BMI or unplanned weight loss as predictors of frailty, a U-shaped curve has been documented for BMI where the BMI <18.5 kg/m<sup>2</sup> and BMI > 30 kg/m<sup>2</sup> were both significantly associated with frailty and sarcopenia. The Women's Health Initiative-Observational Study was the first to identify a significant association between obesity and frailty (Fugate Woods et al., 2005), validated in the Women's Health and Aging Studies (Blau, Xue, Michelon, Semba, & Fried, 2005), and documented in other frailty research (Hubbard, Lang, Llewellyn, &

Rockwood, 2010; Stenholm et al., 2008). Another measure of adiposity, waist circumference greater than 102 cm in men and 88 cm in women is another anthropometric measure that has been used as a nutritional indicator and found to be significantly associated with frailty and other adverse health conditions such as metabolic syndrome, osteoarthritis, and falls and fractures (Ensrud et al., 2007; WHO, 2006).

Obesity is increasingly conferred as a significant predictor of frailty because it induces a pro-inflammatory state that influences the pathogenesis of frailty (Blaum et al., 2005; Hubbard et al., 2010; Villareal, Banks, Sinacore, Seiner, & Klein, 2006; Visser, 2011). Adipose tissue, especially abdominal fat, is biologically active and a source of proinflammatory cytokines such as IL-6 and CRP that foster a catabolic state and development of sarcopenia (Blaum et al., 2005; Visser, 2011). IL-6 stimulates production of CRP and increases an inflammatory milieu. Higher weight corresponds linearly with higher CRP (Blaum et al., 2005). In the Third National Health Survey and Nutrition Examination Survey, CRP was higher in obese adults (Visser, Bouter, McQuillan, Wener, & Harris, 1999). Increased levels of inflammatory biomarkers associated with obesity exert catabolic effects on muscle mass. Chronic low grade systemic inflammation reflected in elevated IL-6 and CRP levels is associated with oxidative stress and immunologic and pathophysiologic impairments that lead to muscle wasting, sarcopenia, and frailty (Hubbard & Woodhouse, 2010). Sarcopenia is a muscle wasting disorder that leads to weakness and mobility impairment. Sarcopenia is an important correlate of frailty in obese adults that can be overlooked as a frailty risk factor that leads to physiologic decline and entry into the cycle of frailty (Blaum et al., 2005; Fried, Tangen,

et al., 2001; Visser, 2011). Along with its physiologic consequences, sarcopenic obesity is related participation in decreasingly lower levels of physical activity and reduced effort and energy expenditure. These behaviors are often secondary to obesity-related symptoms such as joint pain, activity-induced dyspnea, poor aerobic capacity and endurance, fatigue, weakness, and urinary incontinence. The cluster of symptoms induced with physical activity leads to further physiologic and physical performance deconditioning and reduction in physical activity. In addition to increasing risk for frailty, obesity exerts widespread adverse systemic consequences on all organ systems.

**Comorbidity.** Chronic diseases and conditions have been described as the “public health challenge of the 21st century” (Centers for Disease Control and Prevention [CDC], 2009). The seven most common chronic diseases are cancer (several types), diabetes, hypertension, stroke, heart disease, pulmonary conditions, and mental disorders. Chronic disease prevalence increases with age but chronic disease precursors and initial manifestations often present at midlife. In 2005, over half of the U.S. population reported one chronic disease, and by 70 years of age, half reported having one or more chronic diseases (CDC, 2012). In the U.S., the number of people with chronic conditions is projected to steadily increase (AMA, 1990; Yach, Hawkes, Gould, & Hofman, 2004). Similarly, marked increase in the number of adults and children with obesity has recently led the American Medical Society to classify obesity as a medical disease at its 2013 annual meeting due to its association with serious medical conditions, especially Type II diabetes mellitus, cardiovascular disease, hypertension, stroke, sleep apnea, metabolic syndrome, osteoarthritis, cancer, and others (American Medical Association, 2013).

Although higher comorbidity is associated with frailty, the relationship between frailty and comorbidity is not completely explained by the number or type of chronic diseases (J. E. Carlson et al., 1998). Among frail elders, 7% have none of the most common chronic diseases, 25% have one, but more than 90% of persons with  $\geq 2$  were not frail (Ahmed et al., 2007). In the Women's Health Initiative-Observational Study ( $N = 4,657$ , age 65–79 years), 78% of frail women had more than two comorbidities compared to 47.4% of the nonfrail women (Fugate Woods et al., 2005). However, 18.1% of nonfrail women had no comorbidity compared to 3.8% of frail women. In the Cardiovascular Health Study, among the 6% who were frail, 46% had comorbidity, but 22% had comorbidity and ADL disability, and 27% had neither ADL disability nor comorbidity (Fried, Tangen, et al., 2001).

The number and severity of chronic diseases contribute to high symptom burden, disability, early onset of mortality, and frailty (AMA, 1990; Fried, Tangen, et al., 2001; Weiss, 2011) and the disabling impact of symptoms increases with age (Klijs, Nusselder, Looman, & Mackenbach, 2011). Fatigue is significantly associated with chronic disease and may play an important role in the cycle of frailty (Avlund, Rantanen, & Schroll, 2006, 2007). Comorbidity and associated symptoms adversely impact BPSS function and increases stress since symptom management can be complex, complete resolution of symptoms is unlikely, and side effects of symptom management may be distressing (Sawatzky, Liu-Ambrose, Miller & Marra, 2007; Whitson et al., 2009).

Identifying frailty is confounded by the overlap of comorbidity, disability, and frailty, where some frail persons may have no readily identifiable indicators of

vulnerability. Thus, considering other factors such as physical activity, nutrition, symptoms, and psychosocial and economic issues and life stressors become more relevant in frailty assessment.

Comorbidity has an adverse effect on immunity that is not found in healthy aging adults. Chronic illness burden is a potential indicator of physiologic aging that is a more reliable than chronologic age in understanding older adults' blunted immune response to infection, sepsis, and vaccination (Castle et al., 2005). Further, many chronic diseases have underlying inflammatory components (Castle et al., 2005). In older adults, higher comorbidity correlates with the magnitude of the immune response due to the effect of comorbidity on altering immune cell response capacity. Research in healthy older adults without comorbidity found that immune function was near normal (Castle et al., 2005). Thus, it is important to consider the number of chronic diseases as well as conditions that have inflammatory or immunologic pathogenesis since frailty risk may increase. In addition, the efficacy of chronic disease management and magnitude of psychosocial stressors should be considered as these factors influence inflammatory and immune reactivity and activation that can accelerate system dysregulation and disproportionately increase risk for frailty.

**Fatigue.** Fatigue is a common symptom in adults. Prevalence estimates vary considerably and can range from 5% to 50% (Alexander et al., 2010; Cella, Lai, Chang, Peterman, & Slavin, 2002). In a cohort of ambulatory assisted-living residents ( $N = 199$ ) where fatigue was measured by the Piper Fatigue Scale, the vast majority (98%) reported at least mild fatigue. However, 40% reported moderate fatigue and 7% reported severe

fatigue (Liao & Ferrell, 2000). In this study, multivariate regression analyses, depressive symptoms, pain, number of medications, and the three-minute walk were significant predictors of fatigue intensity (multiple  $R = 0.68$ ,  $r^2 = 0.46$ ,  $P < .02$ ). Similarly, Avlund et al. (2006) found that tiredness in daily activities was significantly associated with disability in 419 nondisabled 75-year-old persons. In a study to describe the symptoms experienced by hospitalized adults on medical-surgical units using Memorial Symptom Assessment Scale, a self-rating scale of 31 symptoms ( $N = 334$ , mean age, 57 years, range, 18–93 years), the mean symptom count was 9.31 ( $SD = 5.15$ ) and the mean symptom distress rating was 1.8 ( $SD = .84$ ) and mean symptom severity rating was 1.65 ( $SD = .83$ ) based on a scale of one to five (Kris & Dodd, 2004). Higher symptom distress was identified in women and persons who were single. The five most frequent symptoms were pain (74%), dry mouth (67%), lack of energy (58%), difficulty sleeping (55%), and feeling drowsy (50%). Lack of energy was ranked third for symptom distress (57%).

Fatigue is reported almost twice as often in women compared to men. Self-reported fatigue may vary less by age since younger adults may be more physically active, be employed, and have family responsibilities, which imposes high demands on physical activity. Older adults may report less fatigue because they may become more sedentary and progressively reduced physical activity levels to minimize activity-induced fatigue. Consequently, deconditioning and exercise intolerance progresses as fatigue increases. Thus, self-reported fatigue might not vary considerably across the lifespan since as people age, adjustments in types of activity and the intensity, duration, and frequency is often adjusted to accommodate reduced capacity and more sedentary

behavior. However, self-reported fatigue is more likely to differ when persons of different ages are challenged to perform the same activity with standardized procedures and guidelines for intensity and duration (Hardy & Studenski, 2008).

Fatigue is a normal response to physical exertion or cognitive or emotional strain but is considered abnormal when it is persistent and not relieved by rest, when it interferes with usual function, leads to restriction of daily activities, and is emotionally distressing. Fatigue is associated with chronic disease, acute illness, physical deconditioning, and frailty. Definitions of fatigue and descriptors in fatigue assessment instruments vary widely (Alexander et al., 2010). Terms used to describe fatigue include tiredness, exhaustion, physical or mental weariness, dullness, heaviness, listlessness, lethargy, depleted, drained, debilitated, devitalized, bushed, and petered out. Phrases include slow moving, inability to get going, and frequent need to rest. Many definitions include low energy, based on the premise that fatigue may be a disorder of energy imbalance, characterized by the term fatigability, or the relationships between activity level, capacity for activity, the tolerable rate and intensity of activity before fatigue is experienced, and the point at which activity must be reduced or stopped because fatigue is intolerable and exhaustion has been reached (Alexander et al., 2010; Hardy & Studenski, 2008). Fatigability is relevant in frailty because slowing down and reducing physical activity has a global impact on biologic function and physical performance.

Fatigue is a central feature of frailty. Fried, Tangen, et al. (2001) defined a frailty phenotype as a clinical syndrome consisting of five criteria, where each criterion impacts certain biologic parameters and physical performance that represents a hierarchical

configuration of body system integration and functioning that influences level of fitness or frailty. The cycle of frailty is the cumulative effect of an iterative pattern of low level of physical activity, poor nutrient intake, weakness, muscle atrophy, diminished bone density, and fatigue. Low physical activity and poor nutrition contribute to reduced metabolic rate, energy expenditure, and fatigue. As a consequence, there is down-regulation of physiologic systems and oxygen utilization, which leads to less physical activity, muscle wasting, weakness, and greater fatigue and fatigability. Chronic disease can also adversely influence these processes. Fatigue is a strong predictor of functional limitations, disability, mortality, and other adverse outcomes in young-old and old-old populations (Avlund et al., 2006, 2007).

Xue, Walston, Fried, and Beamer (2011) examined individual Fried Frailty criteria in the Women's Health and Aging Studies II cohort. Weak hand grip strength was the most common frailty criteria but was least predictive of incident frailty. In 76% of the sample, weakness, slow gait speed, and low physical activity preceded fatigue/exhaustion and weight loss. Progression to frailty was not influenced by the number of criteria present. Incident frailty was three to five times more likely in women presenting with fatigue/exhaustion or weight loss, in adjusted models. Similarly, in another cohort of the Women's Health and Aging Study II ( $N = 420$ , 70–79 years, cognitively intact, mild or no physical disability), compared to nonfrail women, those who were prefrail at baseline had a statistically significant threefold higher risk of developing frailty (Xue et al., 2008). Weakness was the most common initial manifestation of frailty, but fatigue/exhaustion and weight loss identified women who were most at risk for transition to frailty.

In a study of community-living older adults to examine tiredness and its impact on function ( $N = 496$ , 65 years and older, cognitively intact or mildly impaired, can walk four meters, gait speed between .2 and 1.3 meters per second, three-year follow-up), 44% reported feeling tired most of the time (Hardy & Studenski, 2008). Tiredness was assessed by one question that asked if during the past month, did the person feel tired most of the time. Of those reporting tiredness, 16% indicated that tiredness did not affect their function, 29% reported their function was affected a little, 29% moderately, and 26% quite a lot. Tiredness was associated with female gender, non-white race/ethnicity, certain medical conditions (sleep problems, chronic pain, emotional problems), greater comorbidity, and more depressive symptoms. Tiredness at baseline was associated with worse baseline function, which persisted during three-year follow-up. Functional status impairment persisted in adjusted models for chronic conditions. Those not tired at baseline experienced a similar rate (but not severity) of functional decline.

Sleep disorders such as sleep apnea, insomnia, poor sleep quality, and restless leg syndrome may contribute to fatigue through metabolic and energetic abnormalities (Alexander et al., 2010). Sleepiness is commonly reported in the the context of fatigue. Underlying mechanisms of fatigue are not well understood but hypotheses are that it is associated with dysregulation of physiologic systems, early manifestations of subclinical disease, inflammation, increased biologic effort to maintain homeostasis, mitochondrial dysfunction, changes in white matter in the brain and neurological aberrations, and oxidative stress (Alexander et al., 2010; Avlund et al., 2006; Hardy & Studenski, 2008).

Fatigue is ubiquitous in health and illness states across the life span and should not be dismissed as “just an unpleasant symptom” (Hardy & Studenski, 2008, p. 1391). Fatigue is poorly recognized, under-treated, and contributes to poor quality of life and considerable risk for frailty (Liao & Ferrell, 2000).

**Urinary incontinence.** Urinary incontinence (UI) is a common problem in adults that becomes more prevalent in men and women at midlife and with advancing age. Higher rates of UI are found in women compared to men due to anatomic differences and consequences of vaginal delivery and multiparity. In older adults, UI is often due to functional impairments, comorbidity, and medications but lifestyle issues such as under-hydration, caffeine consumption, and constipation are influential factors that are treatable. Symptoms associated with different types of UI include urinary urgency, frequency, nocturia, nocturnal enuresis, leakage during physical activity or increased intra-abdominal pressure (cough, sneeze, bend over, lift heavy object). UI is with bladder outlet obstruction and urinary retention with overflow urine leakage that is commonly due to an enlarged prostate gland in men or cystocele in women (DuBeau, Kuchel, Johnson, Palmer, & Wagg, 2010; Gammack, 2004).

Negative psychosocial consequences and reduced quality of life attributed to UI have been well documented (Bogner, 2004; Bogner & Gallo, 2004; Bogner, Gallo, Sammel, Ford, Armenian, & Eaton, 2002; de Vries, Northington, & Bogner, 2012). UI is also associated with high symptom burden (Walke, Gallo, Tinetti, & Fried, 2004). UI is an important factor in decisions about nursing home admission since this condition can be challenging and burdensome for individuals to manage and creates

additional stress for caregivers. UI is considered a syndrome with multiple interacting risk factors such as age-related changes in urinary tract structure and function, comorbidity, and lifestyle behaviors. Common pathways between these factors produce accumulated effects in association with other impairments that arise from or impact systems outside of the lower urinary tract (DuBeau et al., 2010). UI is multifactorial, has a range of defining characteristics, etiologies, and symptom manifestations, and is influenced by medical conditions and situational factors (Inouye et al., 2007). This complexity supports the concept that there are potential shared risk factors between UI and other syndromes such as falls, functional decline, mobility impairment, delirium, cognitive impairment, pressure ulcers, depression, malnutrition, and others (Ensrud et al., 2007, 2008, 2009; Inouye et al., 2007; Tinetti et al., 1995). UI is associated with recurrent urinary tract infection and frequent hospitalizations in older adults.

In a study to assess relationships between UI and frailty and mortality in two age groups of older adults (Sample 1,  $N = 270$ , 65–89 years; Sample 2,  $N = 300$ , 90–107 years, Italy), UI was independently and significantly associated with both mortality and frailty in those 90 years of age and older (Berardelli et al., 2013). In those 65–89 years of age, the correlation between UI and mortality was related to its correlation with frailty. However, severe UI was correlated with mortality after adjustment for frailty. The overall prevalence of UI in this study was much higher in women compared to men (35.1% and 13.8%, respectively;  $p < 0.001$ ). This finding supports increased attention to incontinence in women since research indicates there is higher prevalent and incident frailty in women. Study findings suggest that UI is related to the homeostatic and physiological decline

associated with frailty. The strong correlation of UI with frailty and mortality warrants attention to UI as an indicator or risk factor for frailty.

In a longitudinal population-based survey of older Mexican Americans ( $N = 2660$ ,  $\geq 65$  years, five states) comparing the strength of association between frailty indicators (ADL, IADL, performance measures: timed walk, timed chair rise, tandem balance) with baseline UI and new-onset incident UI, incident UI was associated with increased risk of more global functional impairment (Miles et al., 2001). Baseline prevalence of UI was 14.1% and at two-year follow-up, new onset incident UI was 11.6%. In adjusted models, prevalent UI was only associated with a 60% increased risk of difficulty walking 8 feet, but not other performance measures. However, incident UI was associated with a twofold increased risk of ADL and IADL impairment, and poor performance on all three performance measures. This study highlights the importance of new onset of UI as a potentially important early indicator for frailty.

Further support for the role of UI as a risk factor or etiologic pathway for frailty was provided by a scientific report from the 4<sup>th</sup> International Consultation on Incontinence (ICS) that provided evidence for multiple pathophysiological mechanisms that link UI and frailty. The ICS committee urged increased attention to early recognition, assessment, and treatment of UI since there are effective interventions for older adults and the very old (DuBeau et al., 2010). Implementation of UI best practices is imperative in hospitalized adults since new onset of UI is common and may be reversible (Roe et al., 2004). There is a gap in knowledge about relationships between UI and frailty in

hospitalized adults and the added value of incorporating systematic UI assessment in frailty assessment (DuBeau et al., 2010).

**Activities of daily living.** Activities of daily living (ADL) refer to basic self-care functions necessary for independent living. The Katz ADL Index is the most widely used ADL tool in health science research and consists of six functions: bathing, dressing, toileting, transferring, continence, and feeding (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963). Disability refers to the inability to fulfill customary and desired roles due to the inability to perform social and work-related tasks independently. The Nagi Disability Scale is based on the disablement model and is widely used in research (Nagi, 1976). The scale consists of activities rated according to level of difficulty and includes: (a) pulling or pushing a large object; (b) bending over, crouching, or kneeling; (c) raising arms over head; (d) picking up or handling small objects with your fingers; (e) lifting something that weights over 10 pounds; (f) walking up or down a flight of stairs; and (g) walking one mile. The Nagi disability model distinguishes disease from impairments or symptoms in the disablement process where symptoms provide the pathway by which disease produces functional limitations and disability (Whitson et al., 2009).

The U.S. Census Bureau reports that disability prevalence was 41% among those over 65 years of age compared to 12.3% in the 16-64 year age group and 6.3% in the 5-15 year age group. Future projections suggest that disability may rise and life span may be shortened due to the increasing incidence and prevalence of obesity and morbidity associated with high body weight (Manton, 2008).

ADL impairment can be a predictor, correlate, and/or outcome of frailty. Mild functional limitations may precede ADL impairment and dependence (Pine, Gurland, & Chren, 2000). Fatigue may be a significant factor in the development of ADL impairment (Avlund et al., 2007). Modification in task performance may occur before functional limitations develop that require adaptation, personal assistance or environmental modifications or assistive devices. In a study of older adults ( $N = 287$ , Northern Manhattan Aging Project/Active Life Expectancy Among Urban Minority Elderly Study), walking habits, self-reported difficulty in various walking activities, and gait speed, report of slowing down over was significantly associated with decline in gait speed at one- and 10-year follow-up (Pine et al., 2000, p. M378). In those reporting slowing down, seven percent developed new difficulty walking indoors, 10% experienced new difficulty walking outdoors, and 19% stopped walking for pleasure. Slowing down was associated with worse self-rated health, lower cognitive function, and increased morbidity especially hypertension, arthritis, and joint/muscle pain.

Preclinical walking disability and unrecognized behavioral adaptations may reflect subclinical physiologic changes that signal early frailty since research suggest that frailty precedes disability and there are only modest correlation between the two (Fried et al., 2005; Pine et al., 2000). For example, in the Cardiovascular Health Study, 21.5% were frail with ADL disability and morbidity (Fried, Tangen, et al., 2001). Among this group, 27% could not complete ADLs and 60% had difficulty with IADLs (Fried et al., 2004). In the Women's Health Initiative-Observational Study, of the 16.3% who were frail at baseline, 5.9% had significantly greater ADL disability, compared to 0.7% in the

nonfrail group (Fugate Woods et al., 2005). In the MacArthur Study of Successful Aging, 28% classified as frail by the CHS Frailty criteria and 39% classified as frail by CHS Frailty criteria plus criteria for cognitive function, subjective weakness, anorexia, IL-6, and CRP, had neither disability nor morbidity (Sarkisian et al., 2008).

Consensus conference expert panels recommend excluding measures of ADL function and disability in frailty assessment since in theory, the two are distinctly different phenomenon, frailty precedes disability, disability can exist without evidence of frailty, and ADL impairment or disability are not requisite criteria for frailty (Abellan van Kan, Rolland, Bergman, et al., 2008; Abellan van Kan et al., 2010; Bergman et al., 2007; Rodríguez-Mañas et al., 2012; Sternberg et al., 2011). In a study comparing different definitions of frailty, a definition based on ADL limitations under-estimated frailty, while the addition of IADL impairment or cognitive limitation provided more clinically plausible estimates suggesting that frailty prevalence can vary considerably if disability is included in the definition (The Canadian Study of Health and Aging Working Group, 2001). Progression of functional decline and disability may not mirror the natural history of frailty (Fried et al., 2005). However, the boundaries between disability and frailty blur at advanced ages. Different causal pathways may contribute to each of their development but over time their co-occurrence has a synergistic impact on the development of frailty.

**Assistive devices.** Assistive devices are prosthetics that enhance physical function in ADLs or IADLs. The need for an assistive device indicates the presence of a gait and/or balance disorder or functional limitation that requires adaptation for self-care, mobility, safety, and independence. Although intended to promote safety, assistive

devices can increase risk for falls and injury (Speechley & Tinetti, 1991). In one study, use of an assistive device prior to hospitalization was associated with decline in walking ability and progressive and irreversible functional decline (Mahoney, Sager, & Jalaluddin, 1988).

**Medication.** Medication usage is common in adults. The number of prescription and nonprescription medications increase with age primarily as a consequence of comorbidity and the need for symptom management. Persons with multiple morbidity often require treatment by several health care providers. Inter-provider communication can be fragmented which adversely impacts medication reconciliation, medication errors, polypharmacy, PIM and risk for adverse drug events, cognitive and functional impairment, falls, adherence problems, and health care utilization (Fulton & Allen, 2005; Hajjar et al., 2007; Inouye et al., 2007; Page, Linnebur, Bryan, & Ruscin, 2010).

Polypharmacy is defined as “the use of multiple medications and/or the administration of more medications than are clinically indicated, representing unnecessary drug use” (Hajjar, Cafiero, & Hanlon, 2007, p. 345). Potentially inappropriate medication (PIM) is defined as the use of medications that are not clinically indicated or pose a hazard to the person (Fulton & Allen, 2005). Certain types of medications are considered high risk or contraindicated in the elderly, and if used, must be used with caution with appropriate monitoring (Hajjar et al., 2007; Murphy, Agostini, Van Ness, Peduzzi, Tinetti, & Allore, 2008; The American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012). In one study, taking two drugs was associated with a 13% risk of adverse drug-drug interactions and taking four drugs increased the risk to

38% (Goldberg, Mabee, Chan, & Wong, 1996). In a study of emergency department visits by older adults, where one-third of visits involved prescription medication, adverse drug events were common (Budnitz, Shehab, Kegler, & Richards, 2007). Limiting numbers of medications may be challenging or counterproductive in persons with multiple chronic diseases (Fulton & Allen, 2005; Page et al., 2010).

**Vision.** Vision problems are common in older adults even in the absence of diagnosed eye disease. Data from the National Health Interview Survey indicate that 17% of adults  $\geq 65$  years report visual problems even when vision is corrected with glasses or lenses (Federal Interagency Forum on Aging-Related Statistics, 2010). Vision impairment has a direct adverse effect on physical function, ADL and IADL performance, disability, social interaction, cognition, depression, falls risk, morbidity, and mortality (Bookwala & Lawson, 2011; Klein, Moss, Klein, Lee, & Cruickshanks, 2003; Klein, Klein, Knudtson, & Lee, 2005; Whitson et al., 2007; Whitson, Ansah, et al., 2010). In the North Carolina Established Populations for the Epidemiologic Studies of Elderly (EPESSE;  $N = 3,878$ ), those with visual and cognitive impairment had three to six times the odds of disability, poorer self-rated health, depression, and comorbidity (Whitson et al., 2007). In adjusted models, visual and cognitive impairment strongly predicted ADL, IADL, and mobility disability. In the National/Social Life, Health, and Aging Project ( $N = 1,178$ , 57–85 years), poor self-rated vision contributed to depressive symptoms by predicting more physical limitations and social isolation (Bookwala & Lawson, 2011). In the Beaver Dam Study ( $N = 2,962$ , 43–86 years), a frailty index that included vision assessment (best-corrected distance visual acuity, contrast sensitivity),

gait velocity, timed chair stands, peak expiratory flow rate, and hand grip strength found that severe frailty was significantly associated with the poorest visual acuity and contrast sensitivity, when controlling for age (Klein, Klein, Knudtson, & Lee, 2003). Using data from direct measurement of vision versus diagnosed ocular disease in the frailty index was based on the premise that frailty is a state of compromised integrated function rather than the result of a specific ocular disease. Including measured visual acuity in frailty assessment may improve prediction of outcomes (Knudston, Klein, & Klein, 2009).

**Falls.** Population studies indicate that the prevalence of falls in older adults is 30%-60% annually, and 10%-20% of falls result in injury, hospitalization, or mortality (Rubenstein, 2006). In community older adults, about 40% will fall at least once a year and one in 40 will require hospitalization (Rubenstein, 2006). In a study of 200 consecutive falls experienced by hospitalized adults on medicine and surgery units, of those who had one fall ( $n = 183$ ), 42% sustained an injury and 8% had moderate to severe injury (Hitcho et al., 2004). The high incidence of falls in older adults and susceptibility to injury due to morbidity and age-related changes (e.g., delayed reflex responses, decreased bone density) can make any fall dangerous (Rubenstein, 2006). Fear of falling may increase fall risk through abnormal alterations in gait and posture and reduced physical activity with resultant muscle deconditioning, weakness, and poor balance (Rubenstein, 2006).

There is substantial evidence for associations between falls, frailty and poor outcomes (Ensrud et al., 2008, 2009; Nowak & Hubbard, 2009; Samper-Ternent R., Karmarkar, Graham, Reistetter, & Ottenbacher, 2012; Speciale, Turco, Magnifico,

Bellelli, & Trabucchi, 2004). In a study of community elderly ( $N = 336$ ), frailty was defined by criteria for three levels: Frail, Transitional (criteria for both frail and vigorous), and Vigorous (Speechley & Tinetti, 1999). The Frail group was older, had more comorbidity, depression, cognitive impairment, functional disability, medications, and a history of falls. At one-year follow-up, the prevalence of falls was 52% in the Frail group, 32% in the Transition group, and 17% in the Vigorous group. In the Frail group, 6% of falls resulted in serious injury compared to 22% in the Vigorous group.

In the Study of Osteoporotic Fractures (SOF) in Older Women ( $N = 6,724$ ,  $\geq 69$  years), frailty was defined by a three-component index based on the CHS Frailty criteria (weight loss, inability to rise from a chair five times without using arms, reduced energy level; Ensrud et al., 2007). Eleven percent of women experienced more than two falls. In adjusted models, frail women had significantly more recurrent falls (multivariate *OR* [*MOR*] = 1.38, 95% *CI*, 1.02–1.88), hip fracture (multivariate hazards ratio [*MHR*] = 1.40, 95% *CI*, 1.03–1.90), and non-spine fracture (*MHR* = 1.25, 95% *CI*, 1.05–1.49). Risk for falls, fracture, and mortality persisted with age and across BMI categories. During nine-year follow-up, 31% experienced non-spine fracture and 10% experienced hip fracture. Frail women were at greater risk for fracture (*HR* = 1.7, 95% *CI*, 1.35–2.15) compared to robust women. Similarly, in the Study of Osteoporotic Fractures (SOF) in Men ( $N = 3,132$ ,  $\geq 67$  years) frail men had a significantly higher age-adjusted risk of recurrent falls (*OR* = 3.0–3.6), disability (*OR* = 5.3–7.5), non-spine fracture (*HR* = 2.2–2.3), and mortality (*HR* = 2.5–3.5; Ensrud et al., 2009). In the Women’s Health Initiative-Observational Study, frailty and intermediate frailty were significantly associated with

hip fracture (adjusted  $HR = 1.6$ ; 95%  $CI$ , 1.2–2.2 and adjusted  $HR = 1.3$ ; 95%  $CI$ , 1.0–1.7, respectively; Fugate Woods et al., 2005).

The Hispanic Established Population for the Epidemiological Study of the Elderly ( $N = 847$ ) found that frailty significantly increased the odds of falls (Samper-Ternent et al., 2012). Falls were associated with female gender, history of falls, functional impairment, single partner status, and poor health. The odds of falling was highest for poor balance ( $OR = 1.49$ ; 95%  $CI$ , 1.15- 1.95), prefrail status ( $OR = 1.36$ ; 95%  $CI$ , 1.11- 1.67), and history of falls ( $OR = 1.26$ ; 95%  $CI$ , 1.15- 1.37).

**Dyspnea.** Dyspnea is defined as difficult or labored breathing and shortness of breath. Dyspnea is a symptom that cross-cuts many medical conditions, lifestyle behaviors, and environmental factors. In a study to examine pulmonary function and respiratory symptoms in older adults ( $N = 2480$ ,  $\geq 65$  years, NHANES III) where 55.4% had a smoking history and 44.2% had respiratory symptoms, at 12-year follow-up, 35% had expired. Poor performance on pulmonary function tests (7.7% to 13.4% of sample) was significantly associated with a higher prevalence of respiratory symptoms and increased mortality (Vaz Fragoso, Cancato, et al., 2009).

COPD has a profound effect on physical activity due to poor lung function, oxygenation, and dyspnea. In a study to examine exercise capacity and lung function in a sample of disabled, frail women ( $N = 547$ ,  $\geq 65$  years, WHAS-I, plus 131 additional women), exercise capacity was lower among the frail compared to nonfrail for all exercise parameters that included exercise testing (seated step test), cardiac function (chronotropic index), pulmonary function (forced vital capacity), and musculoskeletal

function (quadriceps strength; Weiss, Hoenig, Varadhan, Simonsick, & Fried, 2010). In women with poor quadriceps strength, frailty was associated with lower exercise capacity, physical and pulmonary function, and mobility and this effect became stronger as pulmonary function worsened.

Inflammatory biomarkers have been used to evaluate disease severity and treatment response. In a review paper analyzing intervention studies in older adults with various chronic diseases, increased serum CRP and IL-6 levels were associated with poorer physical function, independent of age, gender, race, body composition, and disease status including COPD (Brinkley et al., 2009). For example, in an exercise intervention for COPD ( $N = 160$ , 55–80 years). Elevated plasma CRP level ( $M = 4.3$ , range, 1.9–9.2, normal  $< 3$  mg/L) and slow gait speed were indicators of disease severity, symptoms, poor function, and frailty. In a second study using the Short Physical Performance Battery, COPD was significantly associated poor physical performance and muscle loss, which are important frailty components (Guralnik et al., 2000).

In a study to determine if frailty predicted mortality in persons with and without COPD ( $N = 13,288$ ;  $n = 489$  with COPD,  $n = 12,799$  without COPD), mortality was significantly higher in those with COPD (60.7%) compared to those without COPD (48.1%) at 12-year follow-up (Galizia et al., 2011). As level of frailty increased, mortality increased, from 41.7% -75.1% in those without COPD and from 54.3% - 97% in those with COPD. Increasing frailty scores increased long-term mortality by 34% in those without COPD ( $HR = 1.34$  for each unit of increase; 95%  $CI$ , 1.02–1.81;  $p < 0.05$ ) and by 80% with COPD ( $HR = 1.80$  for each unit of increase; 95%  $CI$ , 1.28–2.53;  $p < 0.001$ ). In

multivariate analysis, both COPD ( $HR = 1.34$ ; 95%  $CI$ , 1.02–1.81;  $p = 0.042$ ) and frailty score ( $HR = 1.69$  for each unit of increase; 95%  $CI$ , 1.42–2.00;  $p < 0.001$ ) were predictive of long-term mortality.

**Poor appetite and anorexia.** Decline in appetite and food consumption is considered normative as people age. Decreased intake is related to decline metabolic rate and caloric needs due to lower levels of physical activity and reduced lean body mass and bioactive muscle which results in reduced metabolic demand. Poor appetite and reduced food consumption is also related to medications that alter taste and smell sensation and cause dry mouth, early satiety, and loss of appetite through central nervous system effects. Anorexia is an eating disorder distinguished by markedly reduced appetite, early satiety and inadequate food consumption, and total aversion to food (MedicineNet.com, 2012). In older adults, anorexia was primarily attributed to chronic disease until Morley and Silver (1988) defined the syndrome “anorexia of aging” to reflect a pathophysiologic origin that leads to malnutrition (as cited in Cornali, Franzoni, Frisoni, & Trabucchi, 2005, p. 354). In later stages of frailty, poor appetite, anorexia, malnutrition, cachexia, and fatigue often coexist (Jeejeebhoy, 2012).

In the SENECA study (Survey in Europe on Nutrition and the Elderly, a Concerted Action), independent-living older adults ( $N = 859$ , 75 to 80 years, from nine countries), inactivity and weight loss were examined to determine if these two frailty criteria analyzed in different combinations were significantly associated with health status, physical function, and frailty (Chin A Paw et al., 2003). Compared to the weight-stable, active reference group, both the inactive, weight losing group and the inactive

group reported significantly more chronic disease, disability, medication use, need for care, and poorer physical performance.

In a study that evaluated relationships between anorexia and physical performance, muscle strength, and functional status in older persons ( $N = 364, \geq 80$  years, iSIRENTE study, Italy; Landi, Russo, et al., 2010) the prevalence of anorexia (loss of appetite, lower food intake) was 20% and all physical performance measures were significantly associated with anorexia. Participants with anorexia had significantly slower walking speed, higher risk of disability, and were more likely to become frail. Poor appetite and anorexia may not be directly associated with disease thus early detection is important since prompt treatment increases the probability of success of nutritional and other interventions. Poor appetite, low nutrient intake, and anorexia are associated with frailty and mortality, thus early attention is warranted (Cornali et al., 2005).

**Pressure ulcers.** Pressure ulcers are important quality indicators in hospitalized adults. A pressure ulcer is localized injury to the skin and underlying tissue that usually occurs over a bony prominence as a result of unrelieved pressure, or pressure in combination with shearing forces, friction, and/or moisture (National Pressure Ulcer Advisory Panel, 2007). Hospital prevalence ranges from 4%- 38% (Armstrong et al., 2008; Bolton, 2007; C. C. Chen et al., 2011; Donini et al., 2005). The CMS and Centers for Disease Control and Prevention (CDC) analyzed Medicare data to identify conditions that were high cost and/or high volume and reviewed evidence-based guidelines to determine conditions that were “reasonably preventable” (Armstrong et al., 2008). Pressure ulcers were the most common complicating condition with 257,412 cases of

hospital-acquired Stage III or IV ulcers costing an average of \$43,180 per hospital stay. CMS changes authorized by Congress in the Deficit Reduction Act of 2005 addressed prevention of medical conditions for which there were evidence-based guidelines (Armstrong et al., 2008). For example, since October 2008, CMS classified pressure ulcers as preventable Hospital-Acquired Conditions (HAC) that will not be reimbursed in accordance with current guidelines.

In a retrospective study of frail hospitalized patients with pressure ulcers, 46.5% resolved, but only 31.2% improved (Donini et al., 2005). Pressure ulcer healing was worse in frail patients. Resolution or improvement in pressure ulcers occurred in 87.2% who showed improved frailty status, but in those whose frailty status worsened, only 27.3% of pressure ulcers improved. Pressure ulcers and frailty are syndromes with multifactorial etiologies and potential shared risk factors (Campbell, 2009; Donini et al., 2005; Inouye et al., 2007). In a study of frailty in older hospitalized adults admitted for abdominal surgery, where frailty was defined by a 39-item deficit accumulation index, the only significant predictor of post-operative complications was the Braden Scale, a validated pressure ulcer risk assessment instrument (R. R. Cohen et al., 2012). The Braden Scale aggregates multidimensional aspects of biopsychosocial vulnerability that may similarly portray the multisystem dysregulation associated with frailty.

**Weakness.** Muscle weakness is a common symptom in older adults and is associated with poor physical function, ADL dependence, disability, and frailty (Avlund et al., 2007; Walke et al., 2004). Weakness is important in older adults with comorbidity due to interactions among multiple pathologic conditions and acute illness that contribute

to mobility impairment and reduced physical activity, functional limitations, disability, and dependence (Whitson et al., 2009). In a secondary analysis of data for three medically-different cohorts of community-living older adults to describe correlations between symptom burden and the impact of symptoms and symptom clusters on mobility function, weakness was significantly associated with frailty across multiple chronic disease groups (Whitson et al., 2009). The three cohorts were defined as the cardiorespiratory fitness cohort ( $n = 15$ ), the vertebral fractures cohort ( $n = 211$ ), and the Parkinson's disease cohort ( $n = 61$ ). Measures included a symptom scale, disease scale, Medical Outcomes Study 36-item Short Form Survey (SF-36) Physical Functioning Scale, the Nagi Disability scale, 10-meter walk time, and timed supine to stand test. The most prevalent chronic disease was arthritis and the most commonly reported symptoms were shortness breath on exertion, pain, memory loss, fatigue, and anxiety. In the fitness cohort, the most explanatory three symptom model was muscle weakness, pain, and shortness of breath at rest, but weakness was the most explanatory single symptom. In these three cohorts, correlations between symptoms and mobility function were as strong, or stronger, than correlations between chronic disease and mobility function (Whitson et al., 2009). This study highlights the importance of symptom assessment that cross-cut multiple chronic conditions. Symptom management must be carefully tailored to reduce symptom burden while minimizing adverse side effects and preventing or immediately addressing treatment consequences that worsen some symptoms or create new ones. Ineffective symptom management may lay the groundwork for a pathway to frailty.

In longitudinal and cohort studies, there is strong support for direct measurement of muscle strength (Bandeem-Roche et al., 2006; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Xue et al., 2008). In a study to examine CRP and four physical performance measures (handgrip strength, timed one-leg stand, gait speed at usual and maximal speed) in community older adults ( $N = 803$ ,  $\geq 65$  years, Japan), high CRP was significantly associated with poor physical performance for all measures: handgrip strength ( $OR = 2.92$ ; 95%  $CI$ , 1.53–5.58), timed one leg stand ( $OR = 1.96$ ; 95%  $CI$ , 1.28–3.00), maximal walking speed ( $OR = 2.46$ ; 95%  $CI$ , 1.23–4.93; Yoshida, Iwasa, Kumagai, Yoshida, & Suzuki, 2010). Handgrip strength and walking speed are significant predictors of frailty (Fried, Tangen, et al., 2001; Fugate Woods et al., 2005).

Chronic systemic inflammation is associated with the aging process and with decline in muscle mass and strength, and weakness. The magnitude of chronic inflammation plays a direct role in age-related decline in physical function and morbidity through release of pro-inflammatory cytokine IL-6, a mediator of the acute inflammatory responses that stimulates hepatic production of CRP (Ershler, 1993). Inflammatory biomarkers have a catabolic effect on muscle mass that contributes to muscle weakness. High serum IL-6 level is associated with high CRP, sarcopenia, muscle atrophy, decline in muscle quality and power, and weakness, factors that are pathologic in the development of frailty (Ershler & Keller, 2000).

Inflammation has a fundamental role in the pathogenesis of frailty. Chronic low-grade inflammation contributes directly, or through intermediary mechanisms, to increase risk factors for frailty. Circulating inflammatory biomarkers such as CRP, hs-CRP, IL-6,

and tumor necrosis factor-alpha (TNF $\alpha$ ) are associated with decreased muscle mass and strength, sarcopenia, weakness, poor physical performance, disability, morbidity, and mortality (Cesari et al., 2004; Ferrucci et al., 2002; Leng et al., 2002, 2007; Maggio, Guralnik, Longo, & Ferrucci, 2006; Reuben et al., 2002; Schaap et al., 2009). Both longitudinal and cross sectional studies have linked poor function and mobility, all-cause mortality, and frailty with high levels of inflammatory biomarkers (Cesari et al., 2004; Ferrucci et al., 2002; Reuben et al., 2002; Puts et al., 2005; Taaffe, Harris, Ferrucci, Rowe, & Seeman, 2000; Walston et al., 2002). High inflammatory biomarkers may be a clinical manifestation of inflammaging, high oxidative stress, and age-related damage that cause cellular and organ dysfunction, processes that are integral in the development of atherosclerosis, osteoporosis, sarcopenia, and others (De Martinis et al., 2005; 2006; Maggio et al., 2006).

**C-Reactive Protein (CRP) and hs-CRP.** CRP is a biomarker of inflammation and an acute phase reactant. An elevated CRP level is a nonspecific indicator of inflammation and is associated with the pathogenesis of disease. An acute phase response with rapid increases in CRP occur in conditions associated with inflammation, bacterial, viral, or fungal infection, trauma, tissue injury, tissue necrosis, malignancy, and autoimmune disorders. These conditions cause release of IL-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver. An elevated CRP level does not diagnose a specific disease since many conditions can increase CRP production. High-sensitivity CRP (hs-CRP) is the same analyte as CRP but newer assay equipment is able to detect CRP at lower levels. Most of the literature on hs-CRP pertains to cardiovascular

risk assessment (Bassuk, Fifai, & Ridker, 2004). CRP is used commonly in inflammatory and infectious diseases. Until new assays for analyzing CRP and hs-CRP became available, the erythrocyte sedimentation rate (ESR) test was used to gauge nonspecific systemic inflammatory activity. This test is used less often because CRP is considered a more reliable acute phase reactant with stable performance under acute and chronic conditions (Pepys & Hirschfield, 2003).

During the acute phase response, CRP levels rapidly increase within two to six hours of the acute insult, reaching peak concentration at 48 hours. CRP has a short half-life of 19 hours (Pepys & Hirschfield, 2003). CRP levels may increase up to 50,000-fold in acute inflammation, such as infection. The rapid rise in CRP is due to a rise in plasma concentrations of IL-6, which is produced predominantly by macrophages and adipocytes. CRP half-life is constant under all conditions of health and disease since serum concentrations are determined by the rate of production which reflects the precipitating cause (Pepys & Hirschfield, 2003). Surgery increases CRP levels but CRP returns to baseline during uncomplicated post-operative recovery within eight days (Pepys & Hirschfield, 2003). Since 1973, assessment of serum CRP has been advocated as an objective measure of inflammatory and infectious disease activity, progression and severity, and response to treatment (Otterness, 1994).

The reference range for normal CRP is  $< 3$  mg/L. CRP between 3-10 mg/L suggests chronic inflammation. CRP  $> 10$  mg/L indicates significant inflammatory disease (most often infectious or autoimmune) although higher levels can be detected in genetically predisposed individuals. The reference range for hs-CRP is 1-3 mg/L, but

normal assays can be .1 mg/L or undetectable. High levels of CRP and hs-CRP are associated with cardiovascular risk (Ndumele et al., 2006). Greater than half of adults 55 years of age and older have hs-CRP levels > 2 mg/L and 95% have levels < 10mg/L (Windgassen, Funtowicz, Lunsford, Haris, & Mulvagh, 2011).

African-Americans have higher baseline CRP and hs-CRP levels compared to Whites. In a study of middle-aged African American men and women, there were strong, independent associations of higher CRP and poor physical performance, upper and lower extremity limitations, and disability, independent of chronic disease in adjusted models (Haren et al., 2010). Higher CPR or hs-CRP levels were associated with multifactorial processes that affected physical, cognitive, social, emotional, and behavioral decline.

CRP levels increase with age and in the context of chronic disease, chronic low-grade inflammation (e.g., periodontitis, cytomegalovirus), lifestyle behaviors (low physical activity, smoking, stress associated with inadequate social support), high antigenic load, and alterations in the immune system (Cesari, 2003a, 2003b; Ford, Loucks, & Berkman, 2006; Nielsen et al., 2007). In the InCHIANTI study ( $N = 871$ ,  $\geq 65$  years, Italy) elevated inflammatory cytokines IL-6, CRP, and IL-1 receptor antagonist were associated with poor muscle strength and sarcopenic obesity in adjusted models (age, sex, education, smoking, physical activity, comorbidity; Schragger et al., 2007).

In the Cardiovascular Health Study, elevated CRP levels independently predicted incident frailty at nine-year follow-up (Barzilay et al., 2007). In the Longitudinal Aging Study of Amsterdam (LASA) study, moderately elevated CRP was associated with incident frailty (Puts et al., 2005). In a sub-cohort of the Cardiovascular Health Study ( $n$

= 3141, 69–74 years, nonfrail, no inflammatory disease, nine-year follow-up), elevated WBC, CRP, and IL-6 were each significantly associated with incident frailty, but only CRP remained significant in adjusted models (Barzilay et al., 2007). In the Women's Health Initiative-Observational Study, higher WBC counts and IL-6 levels were independently associated with prevalent frailty (Fugate Woods et al., 2005).

In a prospective study of frailty in older adults ( $N = 1,720$  at inception,  $\geq 65$  years,  $n = 1,509$  at three-year follow-up, Longitudinal Aging Study Amsterdam [LASA] study), the association of CRP, IL-6, serum of 25-hydroxyvitamin D [25(OH)D], insulin growth factor-1 (IGF-1) and frailty was investigated (Puts et al., 2005). Frailty was defined by the presence of three of nine multidimensional indicators. At baseline, the 19% who were frail had significantly higher CRP and lower 25(OH)D levels. In adjusted models, low 25(OH)D but not CRP remained significantly associated with frailty. Incident frailty was 14.1% in those who were nonfrail at baseline. In adjusted models, incident frailty was significantly associated with moderately elevated CRP (3-10 mcg/ml) ( $OR = 1.69$ ; 95%  $CI$ , 1.09–2.63) and low 25(OH)D ( $OR = 2.04$ ; 95%  $CI$ , 1.01–4.13). Neither IL-6 nor IGF-1 were associated with frailty.

In the longitudinal InCHIANTI study of community older adults ( $N = 716$ ,  $\geq 65$  years, Italy), an index of seven serum biomarkers associated with up-regulation and down-regulation of inflammation was assessed for associations with mobility and frailty (Stenholm et al., 2010). Increased up-regulation of IL-6, CRP, and other inflammatory mediators was significantly associated with slower gait speed and low physical activity and a 32% increase in the odds of being frail. CRP level was borderline significant but

IL-6 was significantly associated with frailty. Grip strength was evaluated in relation to biomarkers that have catabolic effects on muscle strength: CRP, IL-6, IL-1 receptor antagonist (IL-1RA), TNF- $\alpha$  receptor 1, dehydroepiandrosterone sulfate (DHEA-S), insulin-like growth factor-1 (IGF-1), and testosterone. The rate of decline in grip strength was significantly greater as the number of abnormal levels catabolic biomarkers increased. Increased number of elevated catabolic biomarkers predicted muscle strength decline better than a single biomarker, suggesting that systemic catabolic dysregulation is an important mechanism associated with decline in muscle strength and risk for frailty.

Low level of physical activity is significantly associated with elevated levels of inflammatory biomarkers. In from the MacArthur Studies of Successful Aging and the Established Population of Epidemiologic Studies in the Elderly (EPESE), low levels of moderate and strenuous physical activity were related to higher IL-6 and CRP levels, and these findings persisted in adjusted models controlled for age and BMI. IL-6 and CRP significantly correlated with each other and were significantly associated with lower plasma albumin level (Taaffe et al., 2000). High intensity physical activity and exercise has been shown to reduce levels of inflammatory biomarkers while the presence of chronic disease is associated with high levels of inflammatory biomarkers (Brinkley et al., 2009; Mohandas et al., 2011; Walther et al., 2008). In a cross-sectional study of high functioning older adults to determine relationships between physical activity and serum levels of CRP and IL-6 ( $N = 870$ , 70–79 years), higher participation in house/yard work and recreational activity were significantly and independently associated with lower

CRP. Low physical activity and overall sedentary behavior increased risk for frailty (Kaiser, Bandinelli, & Lunenfeld, 2010; Mohandas et al., 2011).

Chronic infection is associated with low grade inflammation. Recent evidence indicates that chronic infection contributes to morbidity and mortality through increased inflammation and its impact on systemic changes that lead to disease and frailty (Schmaltz et al., 2005). In the Women's Health and Aging Study I & II, relationships between chronic cytomegalovirus (CMV) infection, IL-6, and frailty were examined ( $N = 724$ , 70–79 years; Schmaltz et al., 2005). In this study, 87% of women were seropositive for CMV infection. In adjusted models, chronic CMV infection was associated with frailty and prefrailty ( $AOR = 3.2$ ,  $p = 0.03$ ; CMV prefrail  $AOR = 1.5$ ,  $p = 0.18$ ). High IL-6 interacted with CMV and significantly increased the risk for frailty but had little effect on frailty when IL-6 levels were low (CMV positive and low IL-6, frail  $AOR = 1.5$ ,  $p = 0.53$ ; CMV positive and high IL-6, frail  $AOR = 20.3$ ,  $p = 0.007$ ; CMV positive and low IL-6 prefrail  $AOR = 0.9$ ,  $p = 0.73$ ; CMV positive and high IL-6 prefrail  $AOR = 5.5$ ,  $p = 0.001$ ; Schmaltz et al., 2005). Frail women had slower gait speed and higher BMI.

Socioeconomic status (SES) and CRP were examined in adults  $\geq 20$  years of age from the Fourth NHANES cohort ( $N = 7634$ ; Alley, Seeman, Kim, Karlamangla, Hu, & Crimmons, 2006). Socioeconomic variation occurred only at very high levels of serum CRP and was strongly significant when family income was at or below the poverty level. Acute illness, chronic conditions, and health behaviors accounted for two-thirds of the association between SES and CRP. African Americans, Hispanics, and women were more likely to have high CRP levels. Study findings support associations of SES stressors

with chronic inflammation and high CRP levels. In a meta-analysis examining acute psychological stress, inflammation, and psychobiological mechanisms underlying hypertension, activation of autonomic and neuroendocrine pathways and sympathetic and adrenal pathways resulted in increased levels of inflammatory biomarkers such as IL-6 and CRP (Stephoe et al., 2007).

In the Fourth National Health and Nutrition Examination Survey, the association between socioeconomic status and CRP was examined in adults over the age of 20 years ( $N = 7,634$ ; Alley et al., 2006). Variation in CRP among different SES groups occurred only at very high levels of CRP ( $> 10$  mg/L). Low SES, defined by family income at or below the poverty level, was associated with significantly higher CRP. Among low SES families, 15.7% had very high levels of CRP ( $> 10$  mg/L) compared to 9.1% of families above the poverty level. Among adults with moderate (1.1–3 mg/L) or high CRP (3.1–10 mg/L), there were no significant differences by SES. African Americans, Hispanics, and women were more likely to have higher levels of CRP. Obesity was the predominant risk factor for every level of CRP above normal. In regression models, acute illness, chronic disease, and health behaviors accounted for about two-thirds of this association. Study findings suggest that very high CRP may be due to factors beyond acute illness and reflect chronic disease, lifestyle behaviors, and other factors associated with low SES.

**Albumin.** Serum albumin is an indicator of health, disease, nutritional status, and inflammation (Corti, Guralnik, Salive, & Sorokin, 1994; Okamura et al., 2008). Serum albumin is the primary protein synthesized by the liver and the most plentiful protein in the blood. It has five main functions: (a) maintenance of 75%–80% of intravascular and

interstitial colloid osmotic pressure in plasma; (b) binding and transport of free fatty acids, calcium, steroid hormones, and certain drugs; (c) free radical scavenging; (d), platelet function inhibition through anticoagulant and antithrombotic effects; and (e) vascular permeability by acting as a reservoir for nitrous oxide and arteriolar relaxation (Don & Kaysen, 2004). The rate of albumin synthesis is affected by nutrition and inflammation (Don & Kaysen, 2004). Adaptive responses are activated when nutritional protein intake is reduced but in the context of inflammation, albumin metabolism is altered (Don & Kaysen, 2004).

Prealbumin is also used to assess protein status. Albumin has a long half-life, about 20 days and a large serum pool, and indicates a stable state of protein deficiency. Prealbumin has a shorter half-life, 2 days, a smaller serum pool, and is more sensitive to acute changes in nutritional status (Beck & Rosenthal, 2002). A shorter half-life permits frequent evaluation of nutritional status. In contrast, changes in albumin level would not be detectable for several weeks thus albumin level provides a longer term picture of nutritional status. Guidelines suggest serum albumin be measured on admission and if low ( $< 3.2$  g/dL), then prealbumin should be tested (Beck & Rosenthal, 2002). In high risk or malnourished patients, prealbumin should be part of nutritional assessment.

Albumin is a negative acute-phase reactant in the inflammatory process. As an inflammatory biomarker, low albumin is associated with increased levels of CRP and other acute phase proteins such as WBC count (Nelson et al., 2000; Visser et al., 2005) and cytokines (Hazzard, 2001). Physiologic mechanisms that lead to alterations in the immune system include normal aging, development and progression of acute illness and

chronic disease, vulnerability to frailty and risk for mortality (Herrmann, Safran, Levkoff, & Minaker, 1992). Under dynamic conditions, activation of a proinflammatory state releases cytokines (IL-6, TNF- $\alpha$ ), positive acute-phase proteins (CRP), and reduce negative acute phase proteins (e.g., albumin; Hazzard, 2001). Low albumin is associated with diseases with an inflammatory component, cancer, stroke, trauma, surgical stress, diseases that cause protein depletion, poor functional status even among healthy adults, and mortality (K. E. Covinsky, Covinsky, Palmer, & Sehgal, 2002; Ferrucci, et al., 2002; Herrmann et al., 1992; Nelson et al., 2000; Okamura et al., 2008; Reuben et al., 2000; Visser et al., 2005).

The prognostic significance of serum albumin and IL-6 in healthy, nondisabled older adults and mortality was examined in older adults with and without evidence of inflammation based on serum IL-6 levels (Reuben et al., 2000). Among older adults with low serum IL-6 (low inflammation), low albumin was associated with an adjusted relative risk of 2.1 for 4-year mortality compared to those with higher albumin (Reuben et al., 2000). Lower albumin level predicted mortality in healthy older adults in the absence of high IL-6. Higher albumin level may have a protective effect in those without inflammation but not in those with evidence of inflammation.

In hospitalized adults, low serum albumin is a significant predictor of longer length of stay, complications, readmission, and mortality (Herrmann et al., 1992). In a study of medical patients ( $N = 1,638$ ,  $\geq 65$  years), high CRP ( $> 5$  mg/L) and low albumin ( $< 3.5$  mg/L) were associated with greater risk of in-hospital death (Iwata, Kuzuya, Kitagawa, & Iguchi, 2006). High CRP and low albumin levels were associated with an

adjusted relative risk of 3.8 for in-hospital mortality compared with the reference group (high albumin, low CRP). When CRP levels were not elevated, low albumin remained significantly associated with in-hospital mortality suggesting that higher albumin level may have a protective effect. CRP and albumin may operate synergistically.

In the Health, Aging, and Body Composition Study, low albumin level was significantly associated with an 18% loss of appendicular skeletal muscle mass at five-year follow-up (Visser et al., 2005). Significant associations were found between low albumin and high CRP and IL-6. Low albumin was associated with sarcopenia and frailty but not low protein intake, morbidity, anti-inflammatory medications, weight training, physical inactivity, or body weight.

Serum albumin was examined as a predictor of disability and mortality among frail elders ( $N = 4,116$ , 71–102 years). A frailty measure was operationalized by five levels of albumin and three levels of physical function (Corti, Guralnki, Salive, & Sorkin, 1994). Pairing of gradients for albumin and disability classified frailty level. Serum albumin levels declined with age, but not all levels were abnormal. The prevalence of low albumin ( $< 35$  g/L) was 2.8% in men, 3.2% in women. The prevalence of normal albumin ( $> 43$  g/L) was 26.7% in men, 23.6% in women. In adjusted models, low albumin was significantly associated with increased all-cause mortality. A strong gradient of mortality risk was found in frail elders based on albumin and disability levels. Within each level of disability, albumin levels  $< 43$  g/L identified persons with excess risk of mortality compared to those with albumin levels  $> 43$  g/L.

Low albumin is an important predictor of mortality, functional decline, and frailty in healthy persons and in those with acute illnesses, chronic disease and malnutrition (Corti et al., 1994; K. E. Covinsky et al., 2002; Visser et al., 2005). Serum albumin may provide clinically important information in frailty assessment since it is a composite marker for aging, malnutrition, inflammation, ADL impairment, sarcopenia, and cachexia (Arques et al., 2008). Low albumin may be overlooked based on beliefs that albumin levels normally decrease with advancing age and in chronic disease despite epidemiologic studies that refute this viewpoint (H. H. Keller, 1993). Further study of the significance of albumin in hospitalized adults is imperative since low albumin levels are prevalent in this population (K. E. Covinsky et al., 2003).

**White blood cell count (WBC).** White blood cells and subpopulations of leukocytes, neutrophils, and monocytes (and others) play a critical role in innate and adaptive immunity and inflammation (Leng, Hung, et al., 2009). WBCs respond to infection through phagocytosis as well as production of antibodies. Normal WBC counts range from 4,300 ( $4.3 \times 10^9/L$ ) to 10,800 ( $10.8 \times 10^9/L$ ), and averages 7,000 ( $7.0 \times 10^9$ ). Counts slightly above or below parameters are considered normal. A WBC count of 3,000–5,000 confers leukopenia, whereas 11,000–17,000 suggests mild leukocytosis.

Elevated WBC count is significantly associated with cardiovascular disease, mortality, and frailty. The Women's Health and Aging Study I (WHAS-I) and Cardiovascular Health Study documented association of high baseline WBC count, excluding acute infection, with increased 5-year all-cause mortality (Leng et al., 2007; Leng, Hung, et al., 2009; Leng, Xue, et al., 2009). In the WHAS-I ( $N = 619$ , age  $\geq 65$

years), significant associations were found for WBC count and inflammatory biomarker IL-6, after adjusting for age, race, smoking, and excluding patients with abnormal WBC (Leng, Hung, et al., 2009; Leng, Xue, et al., 2009).

**Hemoglobin.** Anemia, defined by the World Health Organization (WHO) as hemoglobin concentration < 12 g/dL in women and < 13 g/dL in men, is a common, multifactorial condition in older adults (Beutler & Whaalen, 2006). Anemia increases with age and ranges from 15%-25% in those  $\geq$  80 years living in the community and 48%–63% in those living in nursing homes (Artz, 2011; Landi, Russo, et al., 2010; Patel, 2008). The Third National Health and Nutrition Examination (NHANES III 1991–1994) survey found that 10.2% of community-living older adults were anemic (11% in men, 10.2% in women), and the incidence doubles at 80 years of age (Patel, 2008; Roy, 2011). The severity of anemia is mild with less than 1% of community elders with hemoglobin concentrations below 10 g/dL (Patel, 2008). Anemia is clinically significant as it is associated with falls, reduced muscle strength and physical performance, fatigue, dysmobility, decline in ADL function and cognition, morbidity, and mortality independent of underlying disease (Artz & Thirman, 2011; Roy, 2011). Greater percentages of men and non-Hispanic Blacks develop anemia in old age compared to Whites and women (Patel, 2008; Roy, 2011). In a population-based study ( $N=1,806, \geq$  65 years, 50% Black), the prevalence of anemia was 39% among Blacks and 17% among Whites and was associated with an estimated 90% increased mortality in Blacks and 85% increased mortality in Whites.

Decreasing hemoglobin levels increased mortality independent of comorbidity, behavioral risk factors, nutritional intake, and iron status (Dong et al., 2008). In the Health Aging and Body Composition Study there was no association between anemia and mortality in Blacks however, the population was healthier and higher functioning at baseline (Patel et al., 2007). In a community study of anemia in older adults and mortality ( $N = 775$ ,  $\geq 85$  years, 10-year follow-up, Netherlands), anemia was significantly associated with increased mortality risk. The prevalence of anemia was 17% in women and 28% in men (Izaks, Westendorp, & Knook, 1999).

Anemia may be due to nutrient deficiency, chronic disease, inflammation, and unexplained causes (Patel, 2008). Nutrient deficiencies account for about one-third of anemia (folate, vitamin B12, iron), immune system activation and chronic inflammation accounts for 20%, chronic kidney disease and impaired production of erythropoietin accounts for 8%, and about one-third is unexplained. Morbidity and polypharmacy complicates determination of etiologies of anemia. In NHANES III, two-thirds of those with anemia had two or more chronic diseases (Patel, 2008).

Anemia is associated with chronic inflammation, micronutrient deficiency, high CRP levels, and loss of physical function independent of disease (Ferrucci et al., 1999; Olivares, Hertrampf, Capurro, & Wegner, 2000). In the WHAS-I, chronic disease was defined as CRP  $> 6$  mg/L, WBC  $> 11.0 \times 10^9$ /L, elevated liver function enzymes, infection, liver disease, rheumatoid arthritis, osteoarthritis, and cancer (Semba et al., 2004). The prevalence of anemia was 5.8% and iron deficiency anemia was 3.8%, and the prevalence for was significantly increased in persons with worsening disability.

Low hemoglobin concentration as defined by the WHO criteria is associated with frailty. In the Cardiovascular Health Study, the prevalence of frailty increased as hemoglobin level decreased, even when levels were within normal range (Zakai et al., 2005). Overall, 8.5% were in the lowest hemoglobin quintile for anemia. Mean hemoglobin concentration was 14 g/dL. Men had significantly higher mean hemoglobin concentrations (14.7 g/dL) compared to women (13.5 g/dL). Among Blacks, the prevalence of anemia was higher than in Whites. Low levels of hemoglobin were associated with higher levels of CRP, fibrinogen, and creatinine, and lower albumin levels and WBC counts. Severe anemia was significantly associated with age, smoking, inflammation, BMI, self-reported health, activity level, and chronic disease. Low and high hemoglobin concentrations were independently associated with mortality (Zakai et al., 2005). In older adults, levels of CRP  $> 1$  mg/dL are associated with significantly lower hemoglobin levels (Beutler & Whalen, 2006).

In a study of community older adults ( $N = 30, \geq 70$  years), frail elders had significantly higher IL-6 and lower hemoglobin and hematocrit levels compared to nonfrail elders, indicating systemic inflammation (Leng et al., 2002). There were no differences in other hematopoietic factors (e.g., WBC, platelets). Frail elders had more comorbidity (excluding conditions associated with inflammation or infection; Leng et al., 2002). Anemia may be an independent and potentially modifiable predictor of poor muscle strength and performance, fatigue, activity intolerance, poor cognition, and frailty (Chaves, Ashar, Guralnik, & Fried, 2002; Roy, 2011).

The inflammatory biomarkers CRP, hs-CRP, hemoglobin, WBC are important physiologic parameters in disease, muscle strength, physical function, and frailty. Acute and chronic, cumulative stress and systemic inflammation may be important etiologic factors in frailty whose relationships may be better understood through physiologic measurement of inflammatory biomarkers. Research on relationships between biomarkers, function, disease, and outcomes is growing but there is limited research on biomarkers and frailty (Gruenewald et al., 2009; Szanton et al., 2009; Yao et al., 2011). There is insufficient evidence to confirm which biomarkers, number of biomarkers, or combinations of biomarkers are significantly associated with frailty. Currently, there is no single biomarker or index of biomarkers that predict frailty. The added value of inflammatory biomarkers in frailty assessment in hospitalized adults warrants further research (Walston et al., 2006).

### **Social Domain**

**Social support.** Social support is widely regarded as a valuable resource that consists of tangible and intangible forms of assistance that individuals receive from family and friends. Domains of social support are social networks, social integration, social interaction, social space, informational support, emotional support, illness-related support, and family support (Andrew et al., 2008; Langford et al., 1997; Nicklett et al., 2012; T. E. Seeman, 2000). Positive social support is related to positive mental health and cognitive function (T. E. Seeman et al., 2001). Newsom and Schulz (1996) found that instrumental and emotional support alleviated the effects of disability on depressive symptoms and improved life satisfaction. Lack of social interaction and close personal

relationships are associated with loneliness, depression, home confinement, physical and cognitive function decline, and disability (T. E. Seeman, 1996, 2000; T. E. Seeman & Crimmins, 2001; Simonsick, Kasper, & Phillips, 1998). In a study of women with a history of breast cancer, loneliness was associated with more pain, depression, and fatigued compared to those who were more socially connected (Jaremka, Fagundes, Glaser, et al., 2013). The symptom cluster of pain, depression, and fatigue is common in chronic disease. Loneliness is associated with chronic stress and activation of a proinflammatory state and immune system dysregulation and higher risk for pathological consequences. Subsequent research found that a greater degree of loneliness stimulated increased production of inflammatory mediators and cytokines in response to stress (Jaremka, Fagundes, Peng, et al., 2013). The relationship between loneliness and activation of inflammatory mediators in response to stress may be a physiologic pathway that links emotional states with symptoms and disease states. Other research on the effect of social integration on health outcomes found that social isolation and nonsupportive social interactions can result in lower immune function and higher neuroendocrine and cardiovascular activity while socially supportive interactions have more positive effects (T. E. Seeman, 1996). However, social ties that are stressful or conflicted may exert negative health effects thus the quality of social relationships is important. Lack of social support and poor social integration have been associated with morbidity, coronary heart disease mortality, and poor health outcomes (Loucks, Berkman, et al., 2006; Ranjit, Diez-Roux, Shea, Cushman, Seeman, et al., 2007; Ranjit, Diez-Roux, Shea, Cushman, Ni, & Seeman, 2007; T. E. Seeman et al., 2001). There is strong evidence that social integration

and supportive relationships reduce mortality risk and improve mental health, but direct effects on physical health and disease incidence are less clear (T. E. Seeman, 1996).

In a study of social integration, CRP level and risk for cardiovascular disease ( $N = 14,818$ ,  $\geq 20$  years, NHANES III), analysis of a social network index consisting of marital status, number of contacts with family, friends, and neighbors, religious service attendance, and participation in voluntary organizations and other sociodemographic factors found that elevated CRP levels were significantly associated with men  $\geq 60$  years of age with the fewest social ties compared to men with the most ( $OR = 1.80$ ; 95%  $CI$ , 1.11–2.92), a finding that had a dose-response pattern (Ford et al., 2006). In multivariate adjusted models, social networks and CRP levels were not significantly associated in women or younger men. Further analyses examining chronic diseases, only arthritis, stroke, bronchitis, and possible infection remained significantly associated with social isolation and high CRP levels (but not cardiovascular disease, cancer, myocardial infarction, lupus, heart failure, chronic lung diseases, gout, angina). Gender and generational differences may potentially be explained by qualitative aspects of relationships, gender roles, relationship patterns, and social environment characteristics. Two studies examined social integration and inflammatory biomarkers. In the MacArthur Successful Aging Study (Loucks, Berkman, et al., 2006), social integration was negatively associated with CRP in men but not in women in the least socially integrated quartile compared to the most socially integrated quartile, in adjusted models (age, race/ethnicity, smoking, alcohol, BMI, chronic conditions, cardiovascular disease, depression, physical function;  $OR = 2.23$ ; 95%  $CI$ , 1.05–4.67,  $CRP > 3.19$  mg/L). No

significant association was found between social integration and IL-6. In the Framingham study, social network measured by the Social Network Index was significantly inversely associated with IL-6 in men and women in adjusted models. CRP was marginally associated in men and women, but was not significant in multivariate analysis (Loucks, Sullivan, D'Agostino, Larson, Berkman, & Benjamin, 2006).

Chronic stress, low social position, weak social networks and poor coping ability is associated with poorer physiological function (Glei et al., 2007). A physiologic basis for the effects of social interaction on health outcomes is supported by research demonstrating that social isolation and non-supportive social interactions can lower immune function and increase neuroendocrine and cardiovascular activity, while socially supportive interactions have the positive effect (T. E. Seeman, 1996). In a study of healthy young adults and relationships between positive, negative and competitive social interactions and inflammation ( $N = 122$ ), daily social interactions that were negative and competitive were associated with increased proinflammatory cytokine activity evidenced by higher levels of IL-6 and TNF- $\alpha$  (Chiang, Eisenberger, Seeman, & Taylor, 2012). In the MacArthur Successful Aging Study cohort study, lack of social integration was significantly associated with higher CRP levels in men but not women in adjusted models ( $OR = 2.23$ ; 95%  $CI$ , 1.05–4.76; Loucks, Berkman, et al., 2006). There were no significant associations between social integration and IL-6 in men or women. In the Framingham study, social networks, IL-6, and CRP were examined to explore the biologic pathways to cardiovascular disease (Loucks, Sullivan, et al., 2006). Social

networks were significantly inversely associated with IL-6 in adjusted models, and modestly associated with CRP in men, but not in multivariate analyses.

Studies on factors associated with hospitalization and frequent hospital readmission often emphasize comorbidity, illness severity or instability, and symptom burden as the strongest predictors (Landi et al., 2004; Marcantonio et al., 1999; Williams & Fitton, 1988). However, social factors are also influential (Landi et al., 2004). In an observational cohort study of community-living older adults receiving home health care ( $N = 1,291$ , Silver Network Home Care Project, SILVER-NET, Italy), comorbidity and social factors were examined as predictors of hospitalization and hospital readmission in frail elderly (Landi et al., 2004). During 12-month follow-up, the hospitalization rate was 26%. Social factors associated with hospitalization were living alone ( $OR = 2.59$ ; 95%  $CI$ , 1.82-3.69) and economic hardship ( $OR = 3.01$ ; 95%  $CI$ , 1.75–5.18). Comorbidity and prior hospitalization were also associated with higher risk for hospitalization. Study findings suggest that social factors are influential beyond the medical condition. In other research, greater social vulnerability was moderately correlated with frailty and mortality (Andrew et al., 2008). In the Women's Health and Aging Study I cohort of moderately to severely disabled community women, 23% reported not visiting anyone outside their residence and 17% did not leave home the prior week (Simonsick et al., 1998). Complete social isolation, defined as living alone, having less than weekly social contact with non-household members, and not leaving home in a typical week is rare (3%) in community-living disabled older women and only 8% are homebound and have less than weekly social contact (Simonsick et al., 1998). In this study, social isolation was common. Risk

factors for social isolation were older age, worse ADL disability, not completing high school, lack of transportation, poor hearing, and incontinence. Older African American women living alone were especially vulnerable to home confinement. Low social contact was independent of disability since many severely disabled persons had daily social contact. Other consequences of social isolation noted in this study were depression, poor appetite, weight loss, and deconditioning. The potential adverse consequences of social isolation are germane to frailty.

Social factors and nutritional quality determined by serum carotenoid level were assessed in a cohort of the Women's Health and Aging Study ( $n = 325$ , disabled, one-year follow-up) to determine if baseline social support (emotional support, social interaction, social space, family, change in social support) predicted serum carotenoid levels (Nicklett et al., 2012). Baseline social support did not consistently predict carotenoid level. Leaving home more often predicted increased carotenoid levels; attending few activities predicted decreased carotenoid levels. Change in social support predicted positive and negative change in diet quality, which suggested that social activity and family interaction might play meaningful roles in diet quality. Social support and nutrition are important to consider since poor nutrition is associated with frailty (Bartali et al., 2006).

Frailty is significantly associated with living alone, inadequate social support from family and friends, few social contacts, and lack of someone to provide assistance when needed (Schulz & Williamson, 1993; Fugate Woods et al., 2005). In a population-based study where frailty was defined by a 62-item Frailty Index (FI) ( $N = 2,032$ , age  $\geq 70$ ), more severe frailty was associated with more deficits in social support (Woo,

Goggins, Sham, & Ho, 2005). A higher FI in men was associated with having few relatives or neighbors, little or no exercise, and infrequent or no participation in helping others. In women, having little contact with relatives (but not number of relatives) and lack of participation in community or religious activities was associated with a higher FI.

**Marital status.** Being married has empirically been associated with positive social support and health outcomes, whereas single partner status or living alone has been associated with poor social support and health outcomes. The positive effects of relational qualities support health and well-being and buffer negative psychological consequences of stressful life events, poor health, and disability (S. Cohen, 2004). In the context of illness and disability, the quality of marital or partner social support is dependent on whether the type of support provided meets specific needs. Three types of support were emotional support (expressions of concern, share feelings), instrumental support (help with tasks, offer financial assistance), and informational support (advice, knowledge to help solve problems (S. Cohen, 2004). In a study of older married couples ( $N = 1,532$ ), emotional closeness increased with age and moderated the effects of functional disability through improved self-esteem and reduction in anxiety, depression and mortality (Mancini & Bonanno, 2006). Emotional support was more influential than instrumental or informational support as described by S. Cohen (2004).

The relationships between marital quality and health, illness, disability and potential for caregiver burden are variable (Yorgason, Booth, & Johnson, 2008). Decline in health and development of disability can affect marital quality in many ways, and differ by age cohort. Among younger couples, illness and disability can have a more

negative effect on marital quality, social networks, employment, child rearing, and a view of time that projects a longer future. In contrast, among older couples confronted with illness and disability, there can be a primary focus on the spouse with less emphasis on those factors more salient to younger couples. When chronic illness of a spouse or partner requires caregiving assistance, stress-related caregiver burden can have significant biopsychosocial health risks and other adverse implications for the caregiver. In the MacArthur Studies of Successful Aging, social support among married older adults varied by gender ( $N = 439$ ). Although social support increased over time, men received emotional support primarily from their spouses, but women received more emotional support from friends, relatives and children (Gurung, Taylor, & Seeman, 2003).

In a study of stress related to caregivers for persons with Alzheimer disease ( $N = 116$  caregivers, 54 non-caregiving controls), levels of inflammatory biomarkers were elevated and frailty risk factors (poor health habits, less physical activity, increased morbidity, e.g., hypertension, depression, exhaustion) were increased compared to non-caregiving controls (von Känel et al., 2006).

In a study of the effects of stressors and social support on frailty among older Mexican-Americans over a 12-year period, participants were grouped into one of three trajectories differentiating frailty severity (Peek, Howrey, Ternent, Ray, & Ottenbacher, 2012). The effects of stressors varied by trajectory where health and financial-related stressors were related to increases in level of frailty over time in comparison to the trajectory where effective social support which was related to a slower worsening of

frailty. The role of stressors, social support, and incidence and progression of frailty, particularly in hospitalized adults has not been studied.

**Live alone.** Living alone is associated with greater risk for poor physical and mental health outcomes and frailty. In a study of living arrangements, marital status, and sources of care for IADL and emotional support, married couples tended to receive assistance from their spouse, those who live alone tended to receive assistance from children or friends, and those living with non-spouse others receive more assistance from siblings (Chappell, 1991). The importance of relational and structural characteristics of living arrangements is an important indicator of access to caregiving assistance.

In a study of older adults referred for comprehensive geriatric assessment and frailty assessment ( $N = 302$ ,  $\geq 65$  years), those living alone (41%) were older, received less assistance from informal and formal caregivers, had poorer living and financial conditions, and better cognitive and physical function but worse emotional status compared to those not living alone (Bilotta et al., 2010). Among frail elders (38%), those living alone had a higher prevalence of a new diagnosis of dementia. Frail elders living alone were significantly more likely to experience severe acute disease ( $OR = 303.9$ ,  $p < 0.001$ ), dependence in bathing ( $OR = 62.74$ ), depression ( $OR = 10.43$ ), and incontinence ( $OR = 3.98$ ). Living alone was associated with less personal assistance, more social and financial vulnerability, and greater risk of depression.

### **Psychologic Domain**

**Depression.** Psychological problems such as depression may predispose older adults to frailty through activation of psychoneuroimmunological mechanisms and

biochemical mediators in the brain that affect mood and other biological functions (Fillit & Butler, 2009; McEwen, 2003b). In the Cardiovascular Health Study, the relationship between persistently depressive symptoms and changes in functional disability in older adults was examined in three subgroups: persistently depressed ( $n = 119$ ); temporarily depressed, ( $n = 259$ ); and non-depressed ( $n = 378$ ; Lenze et al., 2005). Persistently elevated depressive symptoms were associated with significantly worse functional disability. In adjusted models, the persistently depressed group had significantly increased functional disability during follow-up (adjusted  $OR = 5.27$ ; 95%  $CI, 3.03-9.16$ ) compared to the non-depressed group. The temporarily depressed group also demonstrated increased functional disability (adjusted  $OR = 2.39$ ; 95%  $CI, 1.55-3.69$ ) compared to the non-depressed group. In the Heart and Soul study ( $N = 667$ , outpatients with coronary heart disease), depressive symptoms predicted higher IL-6 and hs-CRP levels, but higher IL-6 and hs-CRP levels did not predict depressive symptoms (Duivis et al., 2011). After adjusting for health behaviors, associations between depressive symptoms, IL-6 and hs-CRP were not significant, suggesting that health behaviors may mediate depressive symptoms.

In a study to determine if middle-aged persons with depressive symptoms were at higher risk for developing ADL and mobility limitations with advancing age compared to persons without depressive symptoms ( $N = 7,207$ , 50 to 61 years, Health and Retirement Study, 12-year follow-up), 12% had significant depressive symptoms at baseline (K. E. Covinsky et al., 2010). Depressive symptomatology was a significant predictor of ADL and mobility limitations. Those with depressive symptoms were more than twice as likely

to have persistent ADL and mobility limitations (45%) than those who did not (23%). Middle-aged persons with depressive symptoms may be at greater risk for dependence and disability as they age.

Persistent elevation of inflammatory markers due to chronic stress is associated with depression and cognitive decline (Bao, Meynen, & Swaab, 2008; Friedman, Karlamangla, Almeida, & Seeman, 2012). In a study of community adults with chronic illness ( $N = 1,280$ , Longitudinal Aging Study of Amsterdam [LASA] study), depressive symptoms were significantly related to unhealthy lifestyles in middle-aged and older persons (van Gool et al., 2003). Baseline depression ( $n = 176$ ) was significantly associated with smoking ( $OR = 1.71$ ; 95%  $CI$ , 1.17–2.52) and excess alcohol use (relative risk-ratio [ $RRR$ ] = 4.04; 95%  $CI$ , 0.97–16.09). Incident depression ( $n = 155$ ) was significantly associated with decreased physical activity and sedentary behavior ( $RRR = 1.62$ ; 95%  $CI$ , 1.05–2.52), in adjusted models controlling for chronic disease. Smoking, excess alcohol consumption, and low physical activity were associated with chronic inflammation. In the Established Populations for Epidemiologic Studies of the Elderly, a bidirectional relationship was found between depression and disability in older adults (Bruce, 2001). Stable disability (ADL, strength, mobility) and transitions in disability were significantly related to change in depressive symptoms. The onset of disability had stronger effects on change in depression than recovery or improvement in disability.

In a cross-sectional study of community older adults to examine the relationship between depression and frailty, where frailty was defined by the Fried Frailty criteria ( $N = 567$ ,  $\geq 60$  years), depression scores were statistically significantly higher in both pre-

frail and frail groups compared to the robust, nonfrail group (Ní Mhaoláin et al., 2012). In adjusted models, the frail group remained significantly more depressed ( $OR = 4.3$ ; 95%  $CI, 1.5-11.9$ ). In a systematic review of cross-sectional ( $n = 16$ ) and cohort ( $n = 23$ ) studies of depression in later life and frailty, frailty and functional impairment were risk factors for depression (Mezuk, Edwards, Lohman, Choi, & Lapane, 2011). However, none of the studies used standardized tests for depression or accounted for antidepressant use. Positive affect and frailty was investigated in older nonfrail Mexican Americans from the Hispanic Established Populations for Epidemiological Studies of the Elderly cohort ( $N = 1558$ ) frailty (Ostir, Ottenbacher, & Markides, 2004). High positive affect significantly reduced the risk of frailty. During seven-year follow-up, incident frailty was 7.9%. Positive affect may be an important protective factor in frailty since in this study, each unit increase in baseline positive affect score was associated with a 3% decreased risk of frailty in adjusted models. Among African Americans, depression is highly prevalent, under-diagnosed, and under-treated (Wittink, Joo, Lewis, & Barg, 2009). In a study of relationships between faith, spirituality, and depression in African Americans ( $N = 47$ ), a faith-based explanatory model of depression influenced decision-making about treatment (Wittink et al., 2009). Loss of faith was often cited as the cause of depression and “getting faith” was the cure since this restores hope and moral courage. African Americans with untreated depression may be at higher risk for frailty.

**Cognitive function.** Research on relationships between cognitive function and normal aging suggest that only modest changes occur. Impaired cognition is more strongly associated with illness and chronic disease, lifestyle habits (smoking, excessive

alcohol intake, low physical activity, stress-coping responses), brain trauma, and environmental conditions (Cesari et al., 2008; Fulop et al., 2010). In a population-based study of midlife women, cognitive function was significantly related to physical function (Ford et al., 2010). Inflammation is a component of atherosclerosis and small vessel disease that leads to ischemia in the white matter of the brain, increasing risk for stroke, heart failure, Alzheimer's disease, Parkinson's disease, cognitive impairment, and depression. The pathogenesis of inflammation and activation of inflammatory biomarkers exert detrimental physiologic effects on brain function and cognition.

Cognitive impairment is associated with frailty. In the French Three-City Study ( $N = 6,030$ , 65–95 years, four-year follow-up), Ávila-Funes et al. (2009) added the Mini-Mental Status Exam (MMSE) and the Isaacs Set Test (IST) to the Fried Frailty criteria to determine if frailty prediction improved. Overall frailty prevalence was 7%, similar to the CHS study (Fried, Tangen, et al., 2001). Among the nonfrail, prefrail, and frail groups, cognitive impairment was present in 10%, 12%, and 22%, respectively. Lower MMSE and IST scores did not predict mortality but were significantly associated with frailty. In adjusted models, cognitively-impaired frail persons were significantly more likely to develop ADL and IAD disability, and had a small increased risk of incident mobility disability and hospitalization. Incident dementia was greater in those with cognitive impairment in all frailty groups.

Rothman et al. (2008) examined if three Fried Frailty Index criteria plus tests for cognitive function (Mini-Mental State Exam) and depression (CES-D Scale) independently predicted adverse outcomes in non-disabled community older adults ( $N =$

754,  $\geq 70$  years, 96-month follow-up). Baseline prevalence for frailty criteria was highest for muscle weakness (54%) and slow gait speed (43%), followed by low physical activity (31%), depressive symptoms (22%), weight loss (23%), exhaustion and fatigue (13%), and cognitive impairment (11%). In adjusted models, slow gait speed, low physical activity, and weight loss were independently associated with disability, nursing home discharge, and mortality. Cognitive impairment was significantly associated with disability ( $HR = 1.82$ ; 95%  $CI$ , 1.40–2.38), nursing home discharge ( $HR = 2.64$ ; 95%  $CI$ , 1.75–3.99), and mortality ( $HR = 1.54$ ; 95%  $CI$ , 1.13–2.10). During follow-up, the prevalence of cognitive impairment nearly doubled, but slow gait speed, low physical activity, and weight loss changed little. Cognitive assessment improved predictive validity of the CHS (Fried, Tangen, et al., 2001) definition of frailty.

In the Canadian Study of Health and Aging ( $N = 2,305$ ,  $\geq 70$  years), three frailty instruments, the Frailty Index-Comprehensive Geriatric Assessment (FI-CGA, 47 deficits), Clinical Frailty Score, and Fried Frailty Index, were used to classify frailty and determine their ability to predict changes in cognition and mortality (Mitnitski et al., 2011). Cognitive function was assessed by the Modified Mini-Mental State Exam. Change in cognitive status was strongly associated with baseline cognition and frailty for each frailty assessment instrument. In adjusted models, all three frailty assessments were significantly associated with cognitive decline and mortality. Improvement in cognition was unlikely among those who were frail compared to those who were not frail.

In a study of community older adults ( $N = 475$ ,  $\geq 70$  years, Mexican Study of Nutritional and Psychosocial Markers of Frailty), the Fried Frailty criteria plus a

cognitive function test classified frailty to determine prevalent ADL and IADL disability (Ávila-Funes et al., 2011). In unadjusted models, all criteria except weight loss were associated with IADL and ADL disability. In adjusted models, only low physical activity ( $OR = 3.27$ ; 95%  $CI$ , 1.56–6.85) and cognitive impairment ( $OR = 2.06$ ; 95%  $CI$ , 1.04–4.06) were independently and significantly associated with IADL disability. Only low physical activity was significantly associated with ADL disability ( $OR = 7.72$ ; 95%  $CI$ , 1.28–46.46). Of the modified Fried Frailty criteria, only cognitive impairment and low physical activity were primary contributing factors to either ADL or IADL disability.

In a study of acutely ill hospitalized older adults, cognitive function was assessed using the Short Portable Mental Status Questionnaire on admission and 90 days after discharge to determine if admission screening predicted functional recovery ( $N = 2557$ ) (Sands et al., 2003). On admission, 14% had mild cognitive impairment and 28% had moderate to severely impaired cognitive function or were unable to complete the test due to dementia. Cognitive function was significantly related to ADL and IADL assistance. Cognitive impairment was associated with greater likelihood for nursing home admission within 90 days of discharge ( $OR = 2.8$ ; 95%  $CI$ , 1.8–4.5, mild impairment;  $OR = 6.7$ ; 95%  $CI$ , 4.5–9.8, moderate to severe impairment). Admission screening of cognitive function identified risk for ADL assistance, poor recovery, and nursing home admission.

Delirium, also referred to as acute confusion or altered mental status, occurs among hospitalized adults of all ages. Delirium has been cited as the most frequent complication associated with hospitalization of older adults. Delirium is estimated to occur in 11%–42% of hospitalized patients, may affect up to 50% who are at high risk,

and may be unrecognized in up to 70% (Siddiqi, Stockdale, Britton, & Holmes, 2007). In 10%–30% of older adults admitted to the hospital from the emergency department, delirium is the presenting symptom. Delirium is often not recognized since it may be attributed to acute illness and dementia and may be overlooked or dismissed since it can be difficult to measure. Contrary to common beliefs that delirium is self-limiting and reversible, research indicates that delirium is associated with both short and long term cognitive and functional impairment (M. G. Cole, Ciampi, Belzile, & Zhong, 2009). About 12% of older adults who developed delirium during hospitalization had persistent delirium at discharge (Siddiqi et al., 2007). Delirium is significantly associated with functional decline during hospitalization (Murray et al., 1993; Inouye et al., 2007; Tinetti et al., 1995). Preoperative frailty has been significantly associated with post-operative delirium and other complications related to delirium such as longer length of stay and mortality (Kristjansson et al., 2010; Leung, Tsai, & Sands, 2011; Pol et al., 2011).

Clinical features of delirium include clouding of mental status and fluctuating levels of consciousness, poor attention span and memory, disorientation, and illusions and hallucinations. Delirium is most often associated with hyperactivity and uncontrolled motor behavior and cognitive deficits. Hypoactive delirium is less readily identified since motor behavior is blunted; however, cognitive deficits similar to hyperactive delirium are present (de Rooij, Schuurmans, van der Mast, & Levi, 2005).

C. C. Chen et al. (2011) studied common geriatric conditions in a cohort of hospitalized older adults ( $N = 455$ ). Notably, delirium was not included, however many conditions are risk factors for delirium. Geriatric conditions were highly prevalent, and

included, in descending rank order, visual impairment, polypharmacy, sleep disturbance, anemia, chewing and swallowing difficulties, dehydration, malnutrition, depression, cognitive impairment, and pressure ulcers. Each of these conditions is associated with physiologic vulnerability and increased risk for both delirium and frailty in unstable, medically-compromised hospitalized adults. These and others geriatric syndromes share physiologic pathways and mechanisms with delirium and frailty (Quinlan et al., 2011).

In a retrospective analysis of clinical data from an administrative hospital database to describe admission presentation of delirium for four categories of diagnosis related group (DRG) hospitalizations: pneumonia, congestive heart failure, urinary tract/kidney infection (UTI), and lower extremity orthopedic surgery (LEOS; Lin, Heacock, Bhargave, & Fogel, 2010). The prevalence of delirium in the cohort was 0.8% and 59% had an admission diagnosis of delirium. Admission diagnosis of delirium was strongly associated with dementia ( $AOR = 0$ ; 95%  $CI$ , 5.8-6.3) and with adverse drug effects (ADEs;  $AOR = 4.6$ ; 95%  $CI$ , 4.3, 5.0). After admission delirium was more strongly associated with ADEs ( $AOR = 22.2$ ; 95%  $CI$ , 20.7-23.7). On admission, the UTI DRG had the greatest proportion of patients presenting with delirium on admission. After admission, delirium was more common in the LEOS DRG group along with increased proportions in the UTI DRG group. In this study, the role of ADEs is important to note since polypharmacy is common in older adults and is often unavoidable in patients with multiple morbidity, greater symptom burden, in addition to acute illness, trauma, or need for surgery that precipitated hospitalization that may require new medications in addition to medications needed for chronic disease and symptom management. Study findings

highlight the importance of recognition of delirium on admission and initiating early treatment and carefully monitoring medication regimes.

In a systematic review of persistent delirium in hospitalized patients 50 years of age and older to determine its frequency and prognosis, failure to recover from delirium after discharge was documented in a high percentage of patients (M. G. Cole et al., 2009). In analysis of original research on persistent delirium (18 studies, 1,322 patients with delirium), the combined proportions of patients with persistent delirium at discharge, and one, three, and six month follow-up was 44.7% (95% *CI*, 26.8%, 63.7%) at discharge, 32.8% (95% *CI*, 18.4%, 47.2%) at one month follow-up, 25.6% (95% *CI*, 7.9%, 43.4%) at three months, and 21% (95% *CI*, 1.4%, 40.6%) at six-months. Poor outcomes including mortality, nursing home placement, and impaired function and cognition were consistently worse in patients with persistent delirium compared to patients who had recovered from delirium.

In a prospective cohort study of patients admitted to geriatric/medical wards in nine teaching hospitals ( $N = 870$ ,  $\geq 85$  years, two-year follow-up [SAFES cohort: Frail Elderly Subject: Evaluation and Follow-up], France) a Mortality Risk Index was constructed to characterize frailty risk groups using comprehensive geriatric assessment, physical performance measures, nutritional assessment, comorbidity index, pressure ulcer risk assessment and sociodemographic data (Dramé et al., 2008). Three frailty risk groups were classified by the sum of points for weighted risk factors (theoretic range, 0–10). The mean score was 4 ( $SD = 2$ ; range = 0–10). The High risk group scored  $\geq 6$  points (17%), Medium risk group, 3–5 points (56%), and Low risk group, 0–2 points (17%). The

prevalence of delirium was 20%. Significant mortality predictors using this frailty schematic were age over 85 years, delirium, ADL dependence, malnutrition risk, high comorbidity, living in an institution, and female gender. Mortality rate increased in higher levels of frailty risk groups. Delirium was a significant mortality predictor in both bivariable and multivariable analyses.

In a prospective study of hospitalized older adults to examine relationship between delirium and frailty and mortality ( $N = 273$ ,  $\geq 75$  years) where frailty status was measured by a Frailty Index (FI) consisting of 33 deficits and determination of “fit” or “frail” status (Eeles, White, O’Mahony, Bayer, & Hubbard, 2012). Scoring was determined by computations based on the presence of deficits in relation to the total number of deficits in the FI. Scoring ranged from 0 (no deficits) to 1.0 (all 33 deficits) where 0.25 was the cut-point score that differentiated patients who were either “fit” or “frail.” Forty-one percent ( $n = 111$ ) were frail. Delirium was identified in 37% ( $n = 102$ ; mean FI = 0.33) and excluded in 63% ( $n = 171$ , mean FI = 0.18;  $P < 0.005$ ). In “fit” patients with delirium, median survival was 359 days (95% CI; range, 118–600) compared with 88 days for those who were “frail” with delirium (95% CI; range, 5–171;  $P < 0.05$ ). Study findings determined that delirium was associated with the higher levels of frailty based on higher FI scores. Mortality associated with delirium alone was poor; however, the presence of both frailty and delirium was associated with a worse prognosis.

Several studies document failure of nurses to recognize delirium in hospitalized older adults. In a study comparing staff nurse and nurse researcher ratings of patients for the presence of delirium using the Confusion Assessment Method (CAM;  $N = 176$  nurses

paired with a researcher) CAM (Confusion Assessment Method) ratings were completed at least every other day until discharge or delirium was detected by the researcher (Rice et al., 2011). There was poor agreement in observational ratings ( $\kappa = 0.34$ ). Researchers identified delirium in 7% of patients, however, nurses recognized delirium only 25% of the time. Independent predictors of under-recognition of delirium were older patient age, longer length stay, dementia, and hypoactive delirium. Delirium was significantly associated with longer mean length of stay (about five days), however other studies report longer hospitalizations. Study findings have implications for precepted nursing education in detection and assessment of delirium as this has implications for frailty.

**Chronic pain.** Older adults frequently have medical conditions that are associated with persistent or chronic pain. Leong and colleagues (2007) found that comorbidity burden was associated with more severe pain and worse functional status in a pain-clinic cohort. Pain can be insidious, non-acute, and omnipresent (Tak et al., 2009). Symptoms such as pain are a mechanism through which disease impacts functions and well-being (Whitson et al., 2009). Pain may be due to morbidity (musculoskeletal, neurological, visceral, etc.) and can adversely affect mobility, ADL function, level of physical activity, mood, sleep, energy level, and quality of life. Pain scores were more strongly correlated with poor mobility and disability than chronic disease scores. Although pain is common in many chronic diseases and is associated with normal aging changes in body system structure and function, it may not be adequately explained by underlying disease processes (Tak et al., 2009).

The prevalence of chronic or persistent pain among elders in community and institutional settings is estimated at 45%-80% (Maxwell et al., 2008). About 25% who experience daily pain do not receive analgesics, especially minority populations, the very old, and those with cognitive or communication impairment (Maxwell et al., 2008). Ineffective pain management is associated with immobility, low physical activity, fatigue, and depression which can lead to muscle weakness and atrophy, deconditioning, poor balance, falls, sleep disorders, depression, social isolation, functional decline, and increased risk for frailty. In a large retrospective cohort study of pain and comorbid illness ( $N = 1,211,483$  adults,  $\geq 18$  years, with at least one pain condition) pain condition cohorts ( $n = 23$ ) were defined by the first medical diagnosis on administrative claims data forms (Davis, Robinson, Le, & Xie, 2011). The mean number of comorbid pain conditions ranged from 1.39 (cancer, migraine) to 2.65 (multiple sclerosis), about four different pain medications were used, and the majority of participants across pain cohorts were women. Musculoskeletal pain was the most prevalent category ( $> 30\%$ ) and cancer was the least prevalent. There was substantial heterogeneity in types of chronic pain, diseases, mental health disorders (depression, anxiety, others), and sleep problems. The study underscores the importance of determining the presence, magnitude, and impact of pain for different disease conditions on BPSS function and well-being.

Two studies examined pain and frailty. In a cross-sectional study comparing self-rated pain and frailty ( $N = 4,958$ ,  $\geq 65$  years, Canadian Study of Health and Aging), frailty was defined by deficit accumulation and the presence of 33 self-reported illnesses, functional impairments, and health attitudes. Pain was assessed using a five-point verbal

descriptor scale in response to one question, “How much bodily pain have you had during the past 4 weeks?” (Shega et al., 2012). Moderate or severe pain, reported by 35.5%, was independently associated with frailty. This group was more likely to be older, female, and report a depressed mood. Of those reporting moderate or severe pain, 49.8% were frail, 34.1% were prefrail, and 16.2% were not frail. The odds of being prefrail versus frail was greater than twice as likely ( $OR = 2.52$ ; 95%  $CI$ , 2.13–2.99;  $p < .001$ ) and of being frail versus not frail, greater than five times as likely ( $OR = 5.52$ ; 95%  $CI$ , 4.49–6.64,  $p < .001$ ). Frailty was significantly and independently associated with pain.

In study of community-living men on intrusive pain and frailty ( $N = 1705$ ,  $\geq 70$  years, Concord Health in Aging in Men Project, Australia), intrusive pain was assessed by the response to the question, “During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework?” (Blyth et al., 2008). Responses were dichotomous (Not at all; a little bit or moderately; Quite a bit; Extremely). About one-quarter (23.4%) reported moderate to severe pain that interfered with activities. About 15% had four or more chronic diseases but only 2.2% reported opioid use. Arthritis was common (51.7%). The prevalence of frailty was 9.4%; 6.2% were frail with high comorbidity and 40.6% were prefrail. Frailty was significantly associated with pain. Frail men with high comorbidity were more likely to report moderate to severe intrusive pain ( $OR = 3.0$ ; 95%  $CI$ , 1.6–5.5,  $p < 0.0004$ ) after adjusting for depressive mood and arthritis. In frail men with low comorbidity, the association of frailty with pain was statistically significant (adjusting for demographics, arthritis) but not after adjusting for demographics and depressed mood. High comorbidity in nonfrail

men was less strongly associated with pain after adjustment for arthritis ( $OR = 1.5, p < 0.002$ ) and depressive mood ( $OR = 1.4, p < 0.08$ ). Opioid use was highest among frail men, 6.5%, compared to 2.5% of prefrail men and 1.2% of nonfail men.

In the 2004 Health and Retirement Study of community-living adults ( $N = 18,531, \geq 50$  years) the relationship between functional limitations and pain from midlife to old age was explored to determine if significant pain, defined as having moderate or severe most of the time, affected four domains of function (K. E. Covinsky, Lindquist, Dunlop, & Yelin, 2009). Persons were classified according to mobility (jog 1 mile, walk several blocks, walk one block, unable to walk one block), stair climbing (climb several flights, climb one flight, not able to climb a flight), upper extremity tasks (able to do 3, 2, 1, or 0), and ADL function (could do without difficulty, had difficulty but able to do without help, needs help). In the HRS sample, 24% had significant pain. Those with pain had significantly higher rates of functional limitations than those without pain and were comparable to persons two to three decades older. In adjusted models, across all four functional domains, persons with pain were at significantly higher risk for functional limitation:  $AOR = 2.85; 95\% CI, 2.20-3.69$ , for mobility;  $AOR = 2.84; 95\% CI, 2.48-3.26$ , for stair climbing;  $AOR = 3.96; 95\% CI, 3.43-4.58$ , for upper extremity tasks; and  $AOR = 4.33; 95\% CI, 3.71-5.06$ , for ADL function. For example, regarding mobility, among persons age 50 to 59 years without pain, 37% could jog 1 mile, 91% could walk several blocks, and 96% could walk one block without difficulty. In contrast, among persons 50 to 59 years with pain, 9% could jog 1 mile, 50% could walk several blocks, and 69% could one block without difficulty. The 50 to 59 years age group with pain was

similar in mobility limitations to the 80 to 89 years age group without pain. Pain may be a critical component in the cycle of frailty through mobility limitations that lead to physical inactivity, decreased energetics, metabolism and appetite, fatigue, muscle weakness, atrophy, sarcopenia, social isolation, and depression.

**Tobacco use.** Smoking adversely affects multiple organ systems and is associated with poor physical performance and morbidity including cardiovascular disease, myocardial infarction, heart failure, stroke, peripheral vascular disease, cancer, chronic obstructive pulmonary disease, Alzheimer's disease and decline in physical and cognitive function (Almeida et al., 2008; Rapuri et al., 2007). Data from the MacArthur Studies of Successful Aging ( $n = 880$ , a subset of high-functioning older adults [ $N = 1189$ ]) and the Established Populations for Epidemiologic Studies of the Elderly (subset,  $n = 4030$ ) examining inflammatory biomarkers and physical performance, IL-6 and CRP levels were significantly higher in current smokers than nonsmokers and was significantly associated with poor grip strength and slow gait speed (Taaffe et al., 2000). In the Canadian Study of Health and Aging ( $N = 9,008$ ,  $\geq 65$  years), smoking was significantly associated with frailty when adjusting for covariates (Hubbard, Searle, Mitnitski, & Rockwood, 2009). Heavy smokers were more frail, light smokers were intermediate frail, nonsmokers were the fittest. Mortality, cognitive impairment, and worse health were significantly higher among smokers. Smoking, functional decline, and frailty may be linked through chronic inflammatory processes where cigarette smoke activates inflammatory mediators such as CRP and IL-6 (Cesari et al., 2004; Ferrucci et al., 1999)

that leads to muscle weakness, poor physical and pulmonary function, disability, and frailty (Hubbard et al., 2009; Semba et al., 2006).

### **Defining Frailty**

There are multiple definitions of frailty. Frailty has been described using many combinations of signs and symptoms, medical diagnoses, physical, psychological, social, cognitive, and environmental factors and can range from one criteria (e.g., gait speed) to 90 (e.g., deficit accumulation count). The wide spectrum of frailty definitions has been attributed to its recent recognition as a distinct clinical condition and the short time span for scientific research at the bench and at the bedside. Lack of data from primary research makes efforts to reach a consensus definition of frailty challenging (Rodríguez-Mañas et al., 2012). Other barriers include isolation of researchers and clinicians that limit cross-fertilization of ideas and collaborations to explore different perspectives of frailty and the lack of consistent research methodologies to define frailty (Ferrucci et al., 2004; Karunanathan et al., 2009; Levers et al., 2006; Sternberg et al., 2011).

Recommendations from an international consensus conference to determine a definition of frailty using the Delphi method found support for several perspectives: (a) Six domains of frailty were endorsed and included malnutrition, performance measures, gait speed, mobility, cognitive function, mood; (b) The severity of frailty must be assessed, but there was no agreement on severity indicators; (c) There is a relationship between age and frailty but there was no agreement on establishing an age threshold for frailty assessment and if it should be delimited to advanced ages and older adults, adults < 65 years may be at risk; (d) Inclusion of biomarkers in frailty assessment is

recommended but there was no agreement on individual biomarkers or combinations of biomarkers that should be included; and (e) There was disagreement about the timeline for assessing clinical and laboratory biomarkers in the diagnostic process due to lack of evidence (Rodríguez-Mañas et al., 2012). Previously, the Interventions on Frailty Working Group strongly recommended that frailty definitions not include ADL measures of function or disability based on the theory that frailty precedes disability due to subclinical physiologic decline across multiple inter-related systems (Ferrucci et al., 2004). This recommendation was endorsed by the Frailty Definition Working Group (Rodríguez-Mañas et al., 2012). Frailty is presumed to be already present in a preclinical state and evolving. Currently, many frailty assessment tools include ADL assessment since functional decline and impairment are visible and considered a hallmark feature of frailty. CMS has endorsed measurement of ADL function in its definition of frailty (Kautter, Ingber, & Pope, 2008–2009).

There is support for defining frailty as a multidimensional construct that includes biologic factors and physical performance, psychological, social, and spiritual factors (Fillit & Butler, 2009; Gobbens et al., 2010; Markle-Reid & Brown, 2003; Nowak & Hubbard, 2009; Rodríguez-Mañas et al., 2012; Rockwood & Bergman, 2012; Romero-Ortuno et al., 2010; Romero-Ortuno, 2013; Studenski et al., 2004). Qualitative and quantitative research is needed to elucidate relationships and interactions between frailty, gender, race/ethnicity, cultural perspectives, and the environment (Fernandez-Bolaños et al., 2008; Fugate Woods et al., 2005; Hirsch et al., 2006; Walston & Fried, 1999). Table 2 lists selected frailty definitions from quantitative and qualitative research, consensus

reports, concept papers, and textbooks, which illustrate the diversity in frailty conceptualization and defining features.

Table 2

## Definitions of Frailty

Quantitative Research	Source
Independent function when feeling well but experience decline in physiologic function from reduced reserve capacity by a pathophysiologic factor sufficient to instigate a cascade of adverse events that leads to or accelerates age-related deterioration in organ and system function; eventually death ensues. A dynamic balance between biomedical and social components.	Brocklehurst, 1985
Over 65 years of age with one or more functional, cognitive or social impairment.	Matteson & McConnell, 1985
Having any one of 28 risk factors for institutionalization ( $\geq$ 85 years of age, lives alone, mental impairment, ADL limitation, others).	Shapiro & Tate, 1985, 1988
Dependent on others for ADLs.	Woodhouse et al., 1988
A correlate of aging, especially advanced old age and the oldest-old. An ordinary state of health for most people towards the end of life.	Burnside, 1990; Walston & Fried, 1999; Phillipson, 2002; Woodhouse & O'Mahoney, 1997
Poor mental health functioning, cognitive impairment, depression.	Burnside, 1990; Parmelee et al., 1998
Presence of any one criterion: CVA, chronic and disabling illness, confusion, ADL dependence, depression, falls, pressure sore, impaired mobility, incontinence, malnutrition, polypharmacy, bedrest, restraints, sensory impairment, socioeconomic or family problems. Severely frail classified by severe dementia, ADL dependence, terminal illness.	Winograd et al., 1991
Chronically dependent older people with variety of physical and/or cognitive impairments that impede daily function.	Tennstedt & McKinlay, 1994
Severely impaired strength, mobility, balance, and endurance that significantly diminish ADL ability.	Hadley et al., 1993

Table 2. (Cont.)

Quantitative Research	Source
Differentiates frailty as a disease versus as a part of aging based on physics theory related to energy, nutrition, atrophy, disuse.	Bortz, 1993
Frailty occurs when there is diminished ability to carry out practical and social activities of daily living. Proposed 7 parameters for considering frailty: ability to carry out practical and social ADLs; personal and environmental factors that contribute to frailty; continuum from hardiness to frail; frailty as temporary vs permanent; concept of reserve capacity; frailty vs disability; frailty related to age.	I. Brown et al., 1995
Cognitive and mental impairments such as dementia and depression.	M. Collins & Abeles, 1996
Homeostenosis, the exaggeration of age-related physiologic decline causing disruption in biologic function that maintains homeostasis.	Campbell & Buchner, 1997
Consequence of multisystem dysregulation and high allostatic load resulting from chronic stressors that exert wear and tear on the body that impair organ system function over time.	T. E. Seeman et al., 1997
Syndrome involving deficiencies in two or more domains involving physical, nutritive, cognitive and sensory capabilities.	Strawbridge et al., 1998
Diminished function and self-rated health.	Dayhoff, Suhreinrich, Wigglesworth, Topp, & Moore, 1998
Mental frailty differentiated from physical frailty as memory vulnerability in cognitive domain and depression in psychologic domain. Depression may provoke anxiety, memory problems, reduced self-efficacy and confidence in cognitive and psychologic ability.	McDougall & Balyer, 1998
Frailty is based on deficits determined in comprehensive geriatric assessment that warrants admission to a hospital-based geriatric and rehabilitation unit for interdisciplinary care. Focus areas include ADL, IADL, ambulation, transfers, continence, etc. with a detailed scoring system for goal setting and goal attainment.	Yip et al., 1998
State of age-related physiologic vulnerability resulting from impaired homeostatic reserve and reduced capacity to withstand stress.	Fried & Walston, 1998
Midpoint between independence and pre-death, a constellation of many conditions and risk factors rather than a distinct clinical entity.	Hamerman, 1999
Age $\geq$ 85 years, ADL dependence, comorbidity, geriatric syndromes, dementia, $\geq$ 3 falls in past month, delirium (due to pulmonary or urinary tract infection, coronary ischemia, drugs), urinary and fecal incontinence, osteoporotic fractures, failure-to-thrive, neglect, abuse. Although not weighted, some criteria may be more salient than others (e.g., failure-to-thrive).	Balducci & Stanta, 2000

Table 2. (Cont.)

Quantitative Research	Source
Based on a phenotype of 5 criteria (weight loss, weakness, exhaustion, low physical activity, gait speed) where any three or more indicate frailty, 1-2 indicate pre-frail or intermediate frailty, 0 indicates not frail or robust.	Fried, Tangen, et al., 2001
Key indicators: functional abilities (cognition, ADL, IADL), physiologic stress (age, chronic diseases), social support (caregivers). Frailty classified by discharge disposition: (1) return home without services (mild frailty), (2) return home with services (moderate frailty), (3) hospitalization (severe frailty).	Genge, 2001
Loss of adaptive capacity due to a loss of complexity.	Lipsitz, 2004
State of muscular weakness and other losses in function and structure.	Bortz, 2002
Age related alteration in physiology and pathology that leads to vulnerability, loss of physiological reserve, poor medical and functional outcomes; a final common pathway of the effect of disease, disuse, and aging.	Studenski et al., 2004
A cascade representing pre-disability that depends on the interaction of disease processes with normal, age-related processes, lifestyle and environment.	Morley et al., 2006
Age related alteration in physiology and pathology that leads to vulnerability, loss of physiological reserve, poor medical and functional outcomes; a final common pathway of the effect of disease, disuse, and aging.	Studenski et al., 2004
A cascade representing pre-disability that depends on the interaction of disease processes with normal, age-related processes, lifestyle and environment.	Morley et al., 2006
Frailty defined hospitalized heart failure patients by modified Fried Frailty Index, three of five criteria denotes frailty: BMI <18.5 kg/m <sup>2</sup> or >30.0 kg/m <sup>2</sup> ; Albumin <3.8 g/dl; Hemoglobin <13.5 g/dl for men or <12.5 g/dl for women; NYHA class III or IV heart failure and/or ejection fraction <40%; Iowa Fatigue Scale, score >35.	S. Collins, 2007
Physiologic frailty, or “phraily,” covert vulnerability with preserved physical function; is undetected until an acute event exceeds critical threshold. Compare to Functional frailty or “F-frailty,” observable, multifactorial manifestations, due to interaction of aging, disease, functional limitations, disability.	Whitson et al., 2007
Age-related changes in molecular, cellular and physiologic systems, decreased physiologic reserves, reduced stress tolerance; related to chronic inflammation.	Strandberg & Pitkälä, 2007
Increased vulnerability to stressors due to impairment in multiple, inter-related systems, reduced homeostatic reserve and resilience, risk for poor outcomes.	Bergman et al., 2007
A count of accumulated deficits in biologic, physical, cognitive function and other factors that accrue over time.	Rockwood & Mitnitski, 2007

Table 2. (Cont.)

Quantitative Research	Source
Clinical syndrome due to multisystem impairment separate from normal aging.	Abellan van Kan, Rolland, Bergman, et al., 2008
Eligibility for PACE (Program of All-inclusive Care for the Elderly) developed for frail elderly: 55 years and older and certified for nursing home care by appropriate state agency: needs assistance with $\geq 1$ ADLs, moderate cognitive impairment or diagnosed with dementia, dually eligible for Medicare and Medicaid benefits.	CMS, 2006
CMS Frailty Adjustment Model for Medicare payment to hospitals pertaining to preventable 30-day readmission. Frailty defined as difficulty performing ADLs based on objective measurement. Use of standardized ADL count scale improves statistical stability of ADL functional status and outperforms physical function measures (difficulty walking 2-3 blocks, lifting 10 pounds). ADL function superior to medical diagnosis, IADL, or self-report of ADL and assistance needed, since receipt of help is confounded by availability of assistance and cultural influences.	Kautter et al., 2008–2009
Clinical phenotype combining impaired physical activity, mobility, balance, muscle strength, motor processing, endurance, polypharmacy, homebound or institution residence, high risk for disease, disability, hospitalization, death.	DuBeau et al., 2010
A weakened state with reduced reserve capacity that compromises health, functioning, and wellbeing. Frailty and its complications may be avoidable or preventable. Contributing factors may be poor care, neglect or abuse.	Heath & Phair, 2009
Study of hospitalized frail elders, Swedish National Centre of Epidemiology definition: persons $\geq 75$ years of age hospitalized three or more times in past year and has three or more diagnoses according to ICD-10.	Ekdahl, Adersson, & Friedrichsen, 2010
Medically distinct syndrome associated with decreased functional reserve and resilience to stressors.	Fulop et al., 2010
A state of reduced homeostasis and resistance to stress that leads to increased vulnerability and risk of adverse outcomes; seven frailty markers: nutrition (weight loss, poor appetite, BMI), mobility (walking speed $< 1$ m/s, wheelchair), hand grip strength (dynamometer), energy/fatigue (questionnaire), physical activity (3 questions, exercise frequency, intensity), cognitive impairment (MMSE, MoCA), mood (Hospital Anxiety and Depression Scale).	Puts et al., 2010
Frailty is a composite of age-associated disorders and deficits, symptoms, disabilities, and diseases; a systemic indicator of aging and population heterogeneity.	Yang & Lee, 2010
Frailty is accelerated aging.	Weiss, 2011

Table 2. (Cont.)

Quantitative Research	Source
A dynamic process, frequent transitions between frailty states over time.	Gill et al., 2011
A disorder of inter-related physiological systems and gradual decline in physiologic reserve with aging that is accelerated with frailty where homeostatic mechanisms begin to fail. Complex mechanisms of aging promote cumulative decline in system function and depletion of homeostatic reserve and disproportionate changes in health status after minor stressor events.	Clegg, 2011
Frailty is the result of impairment in the physical abilities needed to live independently and is usually the sum of impairments in muscle strength, posture and balance, gait, and bone mass and quality.	NIH, 2012
A multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors. Frailty is differentiated from disability but relationships with comorbidity not established. Operational definition not confirmed but a comprehensive definition was proposed for 6 domains: physical performance, gait speed, mobility, nutritional status, mental health and cognition, biomarkers (not specified). Age threshold was not determined.	Rodríguez-Mañas et al., 2012
Qualitative Research	Source
A lived experience, not biomedical problem. Attributed by others when there is undiagnosed, untreated, or worsening medical condition; may reflect an overwhelmed family and inadequate coping. Frailty is over-medicalized: there is over-emphasis on surveillance, safety, and treatment that creates a sense of disembodiment that separates the person from their medical problems/frailty.	Kaufman, 1994
Frailty is synonymous with disease, disability, and functional decline that interfere with autonomy and ADL function. Frail persons do not see themselves as frail and never use the word frail to describe their health status. Coping was achieved by letting things go, reducing expectations, changing goals, making adjustments, managing losses, accepting there will be good and bad days.	Becker, 1994
Frail means illness and suffering from chronic or acute disease but not necessarily diminished function or self-care. Aging was described as <i>Up in years old</i> (old age), <i>Wore out old</i> (accelerated aging with chronic disease or disability), and <i>Up in years old but not Wore out old</i> (old age but functional). These descriptors imply loss of ability rather than associations with illness or disease, and were similar to but not same as conceptions of frailty. Help seeking is a critical juncture that causes redefining oneself as frail. Blacks perceive themselves as ill or frail only when problems become more severe compared to others of similar circumstances.	Jett, 1994

Table 2. (Cont.)

Qualitative Research	Source
Frailty is a combined ADL and IADL impairment score that represents the contributions and combined effects of medical problems and cognitive impairments that lead to functional decline.	Gealey, 1997
Frailty framed from a feminist, social constructionist perspective in discussions over six months with a task force of older adults from a residential community and low income and disabled elders from apartments. Themes were (a) frailty had no single useful definition; (b) professionals use the term frailty without discomfort but was considered a potentially harmful label; (c) frailty label needs to be changed to focus on independence and inter-dependence community building; (d) use of the term thrive was preferred as it signifies potential for improvement, recovery, and empowerment.	Gray, 1998
Defined as dependence but recognized as a culturally-derived construct, a narrow perspective and label that does not reflect views of frail elders. Efforts to maintain continuity in lifestyle and routines, interdependence, social support preserves autonomy and a level of independence that is based on shifting expectations. These factors are influential in the life of frail elders but does not equate with being frail. These psychosocial issues can be present when one is frail.	Stephenson, Wolfe, Coughlan, & Koehn, 1999
Frail persons do not see themselves as frail in contrast to their care provider. Different patterns of frail elder/provider interactions were illustrative: Partnering (life-encouraging, positive self-image); Disenfranchising (life-discouraging, due to disconnected relationship, feelings of abandonment); Operating in tandem (mutual goals and priorities determined, action plan is collaborative).	Higby, 2001
Frail persons reject the medical label of frailty and its connotations; they do not feel frail since perceived boundaries between frail and nonfrail are blurred. Frailty is contextual, temporal, personal, and relative. Connections between medical and social needs are important.	Grenier, 2002
Frailty characterized by residence in a hostel (assisted living) facility and reporting fatigue for 5 consecutive days. In one-on-one interviews, 5 themes reflected participants' experiences of fatigue: pacing yourself, battling on, hitting rock bottom, feeling safe, moving on. Fatigue created frustration as some participants struggled to maintain daily routines and engage in social activities. Others gave in and made adjustments, lowering expectations and changing routines. Frail elders need support to manage debilitating symptom of fatigue.	Toye, Write, & Rooksby, 2006

Table 2. (Cont.)

Qualitative Research	Source
<p>The social construction of frailty creates dissonance between the aging self and external social messages and health provider assumptions and attitudes. Frail elders do not see themselves as old or frail. Self-image is separate from the provider's objective assessment which focuses on medical issues and does not consider health and wellness and embodiment in the context of the aging experience, morbidity, disability. Adjusting to aging changes and frailty requires negotiating a sense of self and adjusting expectations.</p>	<p>Grenier &amp; Hanley, 2007</p>
<p>Frailty perceptions are based on comparison to referents (older and younger family and friends) and socially constructed symbols for the physical characteristics associated with old age (wrinkles, gray hair, slow, unsteady gait, decline in function and energy). Frail elders do not feel old or acknowledge getting old even when they acknowledge slowing down. Frailty is not always associated with disease or being sick. Aging was described as feeling worn out and/or tired and does not equate with frailty or disease. The biomedical focus on disease over-emphasizes negative aspects of health status, over-medicalizes frailty, and is at odds with the lived experience of frail elders.</p>	<p>Chater, 2002</p>
<p>In a survey of geriatricians, frailty was described as a critical mass of consequences of disease and aging changes manifested as weakness, poor endurance, weight loss, poor nutrition, inactivity, homebound, fear of falling, unsteady gait. Frailty, disease, and disability overlap but frailty can manifest without morbidity or disability. Frailty is represented by poor physical function, disease, and appearance of weakened state with poor tolerance for and recovery from stressors.</p>	<p>Fried et al., 2004</p>
<p>Interviews with experts, clinicians, frail patients, caregivers. Six domains (mobility, balance, strength, endurance, nutrition, neuromotor performance), 7 consequences (medical complexity, healthcare utilization, appearance, self-perceived health, ADLs, emotional and social status). Clinicians highly rated mobility, strength, balance, ADL function, life space. In web-based case studies, clinicians highly rated balance, nutrition, mobility, stamina, ADLs. Frail patients / caregivers rate emotional/social issues highest, clinicians rated them lowest.</p>	<p>Studenski et al., 2004</p>
<p>Interviews with experts, clinicians, frail patients, caregivers. Six domains (mobility, balance, strength, endurance, nutrition, neuromotor performance), 7 consequences (medical complexity, healthcare utilization, appearance, self-perceived health, ADLs, emotional and social status). Clinicians highly rated mobility, strength, balance, ADL function, life space. In web-based case studies, clinicians highly rated balance, nutrition, mobility, stamina, ADLs. Frail patients / caregivers rate emotional / social issues highest, clinicians rated them lowest.</p>	<p>Studenski et al., 2004</p>

Table 2. (Cont.)

Qualitative Research	Source
An empty or catch-all term that has little utility since it does not describe personal experiences or address the chasm between providers who diagnose frailty and frail elders who do not see themselves as frail. Frailty involves balancing, accepting, resisting dependency; these actions are disrupted by medical treatment of disease rather than frailty status. Frailty as a state of dependency is perpetuated by providers and has an adverse impact on frail elder perceptions of autonomy and engagement in decisions about issues that affect them.	Bunk, 2007
Frailty has three dimensions: physical, psychological/cognitive, social. Comorbidity, poor health, walking difficulty, feeling down, anxiety, few social contacts, unable to do things one likes to do. Frailty is inevitable, cannot be prevented or controlled. Frail men focused on physical impact (disease, functional limits, dependence); frail women, on psychosocial impact (feeling down, lonely).	Puts et al., 2007
Frailty was based on opinions of health professional experts and was defined as multi-dimensional and distinct from disability, a dynamic state that affects individuals who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of many factors. Frailty increases the risk of adverse outcomes.	Gobbens et al., 2010a
Frailty defined by count of deficits in Chinese adults $\geq 55$ years of age. Higher counts represent “variable vulnerability” in risk for adverse outcomes among persons of same age. The count of deficits does not consider type, severity, or impact of the deficit on health status and risk of adverse outcomes. Deficit accumulation in persons of the same age is more closely linked to mortality than age alone.	Shi et al., 2011
Frail elders describe themselves “living in the margin” with little recognition of or support for the work of living and dying during the aging process. The aging and frailty experience operates in binary modes: social or health; independent or dependent; living or dying and hinders ways to negotiate smooth transitions. Visible markers of functional limitations and increasing social losses make end-of-life concerns more real. To maintain continuity and grounding with present, frail elders put forth effort to develop and sustain connections to physical environment, routines and social networks.	Nicholson, Meyer, Flatley, Holman, & Lowton, 2012

Despite a preponderance of frailty definitions, many with common themes, no single definition has been adopted for use in research and practice (Karunanathan et al., 2009; Rodríguez-Mañas et al., 2012; Sternberg et al., 2011). Frailty encompasses a

variety of characterizations due to population heterogeneity and situational factors (Rockwood et al., 2000). It has been proposed that a single definition of frailty may not suffice for all populations, settings of care, and applications. Rockwood (2005) suggests that lack of a consensus definition for a frailty “should not be a source of concern” since different definitions may suffice for different purposes (p. 434). The diversity in frailty definitions reflects theoretical perspectives and observations of frailty in different populations and is based on the utility of the definition for application in practice, research, or public policy. However, qualitative literature offers uniquely different perspectives of frailty from persons who have been identified as frail that strikingly contrasts with conventional biomedical perspectives and much of the published literature. These perspectives have not been referenced in published consensus reports that propose definitions of frailty or terminology used to describe frailty status.

Evaluating the psychometric properties of different operational definitions of frailty and cross-study comparisons will be important to advance the science. Romero-Ortuno et al. (2010) note that there is no consensus on age parameters for frailty assessment since frailty relates more to biological age than chronological age, thus frailty research should not be limited to the old nor should frailty be dismissed as a concern in younger populations (Rodríguez-Mañas et al., 2012). From a practical perspective, Rockwood et al. (2000) asserts that there has been successful frailty intervention research without a definitive consensus definition of frailty. There is sufficient evidence for primary and secondary prevention, particularly related to physical activity and nutrition that merits clinical application (Kane et al., 2011).

In general, the literature suggests that a definition of frailty should (a) characterize frailty as multisystem impairment and differentiate it from aging, disability, and morbidity; (b) describe the etiology, instigating factors, typology, natural history, and different trajectories; (c) describe frailty as multidimensional and include biological, psychological, social, and spiritual domains, social determinants, physical environment, life stressors; (d) reflect complex interactions of body and social systems and capture instability and change over time; (e) be comprehensive in order to clarify the nature of dynamic interactions and nonlinear relationships of multiple components, that reflect system complexity and multiple pathways, where no single component is etiologic; (f) heterogeneity in the aging process and reduce emphasis on chronologic age thresholds; (g) facilitate estimation of risk level and prediction of adverse outcomes; (h) outcomes of interest should extend beyond mortality, disability, and other system-related factors and take into account subjective perspectives of frail elders and; and (i) avoid language that suggests ageism, pessimism, or therapeutic nihilism (Abellan van Kan et al., 2010; I. Brown et al., 1995; Clark et al., 2007; Fillit & Butler, 2009; Gobbens et al., 2010a, 2010b; Grenier, 2002; Hogan et al., 2003; Izaks et al., 1999; P. O. Lang et al., 2009; Markle-Reid & Browne, 2003; Perera, Hilmer, & McLachlan, 2010; Rockwood et al., 2000; Rodríguez-Mañas et al., 2012).

Frailty prevalence estimates vary considerably due to differences in theoretical precepts, operational definitions and measurement, population characteristics, and study design. Multiple definitions present a challenge in determining incidence, prevalence, at-risk populations, and outcome prediction (Kane et al., 2011). Lack of conceptual clarity

about frailty and poor concordance of frailty definitions underscores the importance of interpreting frailty research with caution (Pijpers, Ferreira, Stehouwer, & Nieuwenhuijzen Kruseman, 2012).

### **Frailty Perspectives and Prevalence**

Theoretical and conceptual perspectives of frailty vary considerably given the dramatic increase in awareness of frailty as a distinct clinical condition and burgeoning research to determine its etiologic, diagnostic and clinical features (Gobbens et al., 2010b; Hogan et al., 2003; Karunanathan et al., 2009, Levers et al., 2006; Markel-Reid & Browne, 2003). The frailty literature draws attention to the diverse perspectives in frailty conceptualizations and measurement that are appreciated by investigators with different goals and objectives (De Lepeleire et al., 2009). Frailty assessment can vary from one indicator (e.g., gait speed; Purser et al., 2006) to 90 indicators (Rockwood et al., 1999). Five frailty perspectives are summarized below.

#### **Phenotype for Physical Frailty**

Fried, Tangen, et al. (2001) proposed a phenotype of physical frailty defined as a clinical syndrome consisting of five distinct criteria that operate in an iterative, cyclical process. The premise of the cycle of frailty is that certain criteria represent a hierarchical integration of body system functions that reflect the degree of intact homeostasis and level of fitness or frailty. Homeostasis depends upon complex integrative networks among many body systems, sufficient compensatory reserve and capacity, and effective bidirectional system redundancies that permit appropriate physiologic responses to stressors (Fried, Tangen, et al., 2001; Fried et al., 2005, 2009). As deficits such as

physiologic changes associated with advancing age, morbidity, mobility impairment, and functional decline accumulate, physiologic adaptive responses to acute and chronic stressors diminish. When a critical threshold is crossed, compensatory capacity exceeds demand and aggregated physiologic changes permit the evolution and unfolding of subclinical processes that lead to observable manifestations of frailty (P. O. Lang et al., 2009). The trajectory may include transitions from a latent, pre-frail state to intermediate or full frailty when homeostasis and allostasis processes fail (Whitson et al., 2007). There are multiple points of entry into the cycle of frailty. Entry at any point propels a downward spiral and adverse consequences.

Five frailty criteria constitute the Fried Frailty Index: unintentional weight loss, weakness, subjective exhaustion/fatigue, slow gait speed, and low level of physical activity. Three levels of frailty are determined: nonfrail, prefrail, and frail. Frailty is defined by having any three of the five criteria; intermediate frail, having any two criteria; prefrail, one criterion; and nonfrail, none. The phenotype for physical frailty was validated in the Cardiovascular Health Study (CHS), a prospective observational study of adults 65 years of age and older recruited from four U.S. communities ( $N = 5,201$ , final sample 4,735; additional cohort of African Americans,  $N = 687$ , final sample,  $n = 582$ ; Fried, Tangen, et al., 2001). Exclusion criteria were Parkinson's disease, stroke, Mini-Mental Status Exam scores  $< 18$ , and prescriptions for Sinemet, Aricept, or antidepressants. The Fried Frailty Index predicted significantly increased risk for four of five outcomes at seven-year follow-up: worse mobility, worse ADL function, hospitalization, mortality, but not incident falls (Fried, Tangen, et al., 2001). The Fried

Frailty Index has been utilized in other populations in original or modified formats (Alvarado et al., 2008; Bandeen-Roche et al., 2006; Cawthon et al., 2007; Cigolle et al., 2009; Ensrud et al., 2007; Fugate Woods et al., 2005; Graham et al., 2009; Romero-Ortuno et al., 2010; Rothman et al., 2008; Santos-Eggimann et al., 2009; Sarkisian et al., 2008; Semba et al., 2006; Szanton et al., 2009; Vaz Fragoso, Gahbauer, et al., 2009; Wilhelm-Leen, Hall, Tamura, & Chertow, 2009; Xue et al., 2008).

The Women's Health Initiative-Observational Study was the largest study to examine frailty using the CHS Frailty criteria ( $N = 40,657$ , 65 to 79 years, 40 centers; Fugate Woods et al., 2005). A modified version of the CHS Frailty included validated proxy measures for selected criteria. Frailty criteria included muscle weakness and slow walking speed (score,  $< 75$  out of 100 on the RAND-36 physical function scale, counts as two components), exhaustion (score,  $< 55$  out of 100, RAND-36 vitality scale), low physical activity (kilocalories of weekly energy expenditure in lowest quartile calculated from a physical activity questionnaire), and unintentional weight loss  $< 5\%$  during the past two years.

**Studies using the Fried Frailty Index.** In the CHS, the prevalence of frailty was 6.9% and ranged from 3.2% in those 65-70 years to 25% and in those  $\geq 85$  years (Fried, Tangen, et al., 2001). In the Women's Health Initiative Observational Study (WHI-OS) of community women ( $N = 40,657$ , 65–79 years), frailty prevalence was 16.3% compared to 18% in a comparable sample in the CHS (Fried, Tangen, et al., 2001; Fugate Woods et al., 2005). In the Health and Retirement Study ( $N = 11,113$ ,  $\geq 65$  years), 10.9% were frail (Cigolle et al., 2009). In the Women's Health and Aging Studies I and II (WHAS-I,  $N =$

1,002,  $\geq 65$  years, most disabled at baseline; WHAS-II,  $N = 436$ , 70–79 years, least disabled at baseline), overall frailty prevalence was comparable to the CHS study (Bandeem-Roche et al., 2006). In separate analyses of the WHAS-I and WHAS I cohorts, frailty prevalence was 11.6% and 11.3%, respectively (Xue et al., 2008). In the Study of Osteoporotic Fractures of Older Women ( $N = 6,724$ , community-living women,  $\geq 69$  years), 16% were frail (Ensrud et al., 2007). In a study of micronutrient deficiencies using the Women's Health and Aging Study I cohort of community-living disabled women ( $N = 766$ ,  $\geq 65$  years, three-year follow-up), 33% were frail at baseline (Semba et al., 2006). Of 463 nonfrail women who had at least one follow-up visit, 31.9% became frail. Micronutrient deficiencies (serum vitamins A, D, E, B<sub>6</sub>, B<sub>12</sub>, carotenoids, folate, zinc, selenium) predicted frailty. In adjusted models, number of nutritional deficiencies and low serum carotenoids, vitamin E, and vitamin D were associated with higher risk for becoming frail. In a study to examine frailty and kidney disease using data from the Third National Health and Nutrition Survey, a modified Fried Frailty Index identified frailty in 2.8% with moderate kidney disease and 20.9% with severe chronic kidney disease (Wilhelm-Leen et al., 2009). The odds of frailty were significantly increased at all stages of chronic kidney disease, after adjusting for age, gender, race, and chronic disease.

Several multi-country population-based studies used the Fried Frailty Index. In a study conducted in five Latin American cities examining life course social and health conditions and frailty ( $N = 10,661$ ,  $\geq 60$  years, Spanish for Health, Wellbeing and Aging Study; Alvarado et al., 2008) frailty prevalence ranged from 30%-48.2% in women and 21.5%-35.4% in men. Substantial variability in prevalence across cities was attributed to

early life or long term psychosocial, socioeconomic, and environmental stressors. In a study of community adults  $\geq 50$  years in 10 European countries ( $N = 16,584$ , Survey of Health, Ageing and Retirement in Europe [SHARE]), the prevalence of pre-frailty and frailty was 4.1% and 37.4%, respectively (Santos-Eggimann et al., 2009). Women were significantly more frail (5.2%) and prefrail (42%) compared to men, (2.9% and 32.7%, respectively). In those  $\geq 65$  years, 17% were frail and 42.3% were prefrail. Frailty prevalence among older women was significantly higher compared to men: 21% and 11.9%, respectively. More women were prefrail than men: 42.7% and 41.9%, respectively. In this study, all frailty criteria were modified. Questions were substituted for weight loss criteria (poor appetite, eating less), gait speed (difficulty walking 100 meters, climb flight of stairs without resting), low physical activity (frequency, intensity of gardening, cleaning car, going for walk, etc.). Another study examining frailty in the SHARE population-based study in 12 European countries ( $N = 31,115$ ,  $\geq 50$ ), where the SHARE-Frailty Index was developed based on the Fried Frailty Index, frailty prevalence was comparable to the CHS data (Romero-Ortuno et al., 2010).

Investigators have included psychological and social variables, diagnostic tests, and biomarkers in frailty assessment using the Fried Frailty Index. In the Study of Osteoporotic Fractures in Men Research Group ( $N = 5,993$ ,  $\geq 65$  years), dual energy x-ray absorptiometry was added to assess sarcopenia and bone density (Cawthon et al., 2007). Four percent were classified as frail and 40% were prefrail. In a community-based heart failure population ( $N = 169$ ,  $\geq 60$  years) the six-minute walk test of aerobic capacity was added and 25% were classified as frail (Boxer et al., 2008). In a cross-sectional study

in community older adults ( $N = 374$ ,  $\geq 78$  years) to evaluate sleep-wake disturbances and frailty, the Epworth Sleepiness Scale (ESS) and the Insomnia Severity Index (ISI) were added to the Fried Frailty Index (Vaz Fragoso, Gahbauer, et al., 2009). Analysis of sleep-wake disturbances (daytime drowsiness,  $ESS > 10$ ), sub-threshold insomnia (ISI, 8–14), and clinical insomnia (ISI  $> 14$ ), and the Fried Frailty Index classified 41.2% as frail, where 23.8% were drowsy, 32.8% had sub-threshold insomnia, and 10.2% had clinical insomnia. Clinical insomnia and frailty were significantly associated in unadjusted models ( $OR = 2.77$ ; 95%  $CI$ , 1.36–5.67) but not in adjusted models ( $OR = 1.93$ ; 95%  $CI$ , 0.81–4.61). Daytime drowsiness was significantly associated with frailty in adjusted models ( $OR = 3.67$ ; 95%  $CI$ , 0.03–6.61).

Rothman et al. (2008) examined if individual Fried Frailty Index criteria and a measure of cognitive function (Mini-Mental Status Exam) and depression (CES-D Scale) were independent predictors of adverse outcomes in community older adults ( $N = 754$ ,  $\geq 70$  years, 96-month follow-up). Baseline frailty prevalence was highest for muscle weakness (54%) and slow gait speed (43%) followed by low physical activity (31%), depressive symptoms (22%), weight loss (23%), exhaustion/fatigue (13%), and cognitive impairment (11%). In adjusted models, three of the five frailty criteria (slow gait speed, low physical activity, weight loss), were independently associated with disability, nursing home placement, and mortality. Slow gait speed was the strongest predictor of chronic disability ( $HR = 2.97$ ; 95%  $CI$ , 2.32–3.80), nursing home discharge ( $HR = 3.86$ ; 95%  $CI$ , 0.23–6.67) and injurious falls ( $HR = 2.19$ ; 95%  $CI$ , 1.33–3.60). Cognitive impairment was significantly associated with disability ( $HR = 1.82$ ; 95%  $CI$ , 1.40–2.38), nursing home

placement ( $HR = 2.64$ ; 95%  $CI$ , 1.75–3.99), and mortality ( $HR = 1.54$ ; 95%  $CI$ , 1.13–2.10). The prevalence of cognitive impairment nearly doubled during follow-up, while gait speed, physical activity, and weight loss changed little.

In a study of high functioning elders (70 to 79 years, MacArthur Study of Successful Aging), 13 biomarkers were included in frailty assessment. Abnormal biomarker values were scored as one point and the summed score was a measure of allostatic load and multisystem physiologic dysregulation (Gruenewald et al., 2009). Higher allostatic load scores indicated greater physiologic dysregulation and risk for poor outcomes. In regression models, a 1-unit increase in the allostatic load score was associated with a 10% greater likelihood of frailty at three-year follow-up. Similarly, in the WHAS I and II studies ( $N = 728$ , 70 to 79 years), 11 biomarkers were added to frailty assessment to determine associations between allostatic load and frailty (Szanton et al., 2009). At baseline, 10% were frail and 46% were prefrail. Allostatic load ranged from 0 to 8 with 91% scoring 0 to 4. In regression models, a 1-unit increase in allostatic load was associated with increasing frailty in adjusted models ( $OR = 1.16$ ; 95%  $CI$ , 1.04–1.28), supporting association of frailty with physiologic dysregulation.

### **Deficit Accumulation Framework**

The accumulated deficit framework defines frailty as the net effect of the accumulation of deficits in various domains over time that creates physiologic vulnerability and risk for frailty, mortality, and other adverse outcomes. The interaction of aging, disease, symptoms, poor nutrition, inactivity, poor social support, and other factors affects biologic aging and increases vulnerability to minor physiologic and

psychosocial stressors (Rockwood et al., 1999). The physiologic and psychologic burden of deficit accumulation contributes to decrements in function across multiple body systems that when a threshold is exceeded, system redundancies and regulatory functions break down and compensatory reserves decline. Over time, as frailty evolves, vulnerability to stressors increases. Deficit accumulation may characterize the aging process better as an indicator of biologic age rather than chronologic age (Mitnitski, Graham, et al., 2002; Mitnitski et al., 2001; Rockwood & Mitnitski, 2011).

In an early longitudinal study of community-living older adults using this framework, a frailty scale was developed ( $N = 9008$ ; Rockwood et al., 1999). Baseline assessment defined four levels: Class 0 (independent in ambulation and ADLs, continent, cognitively intact); Class 1 (bladder incontinence only); Class 2 (one [or two if also incontinent] if mobility or ADL assistance needed and cognitive impairment but no dementia); and Class 3 (two [three if incontinent] if totally dependent in mobility and transfers and one or more ADLs, incontinent of bowel or bladder, dementia). Frailty was defined by increasing dependency in ADLs and cognitive impairment during follow-up. At baseline, 67% were independent (Class 0), 12% were Class 1, 16% were Class 2, and 5% were Class 3. At five-year follow-up, 24% died, 12% were institutionalized. The frailty scale demonstrated a significant dose-response relationship in Cox proportional hazards modeling (adjusted for age and gender) between frailty level, institutionalization, and mortality. The highest risk level was Class 3.

In the Canadian Study of Health and Aging (CSHA,  $N = 10,263$ ), the deficit accumulation framework was used to describe health issues in the aged (Rockwood et al.,

2005). From clinical exams, a rule-based definition was developed for a Frailty Index (FI) based on a count of 70 deficits (CSHA-I). The FI reflected a continuum for levels of fitness and frailty to stratify older adults based on deficit count and subsequent risk for mortality and institutionalization.

In a study in community older adults ( $N = 66,589$ ), the construct validity of the Frailty Index (FI) was examined to estimate level of fitness and frailty in relation to biological age compared to chronological age. The average value of the FI increased with age in a log-linear relationship. In regression analyses, biological age was more significantly associated with mortality than chronological age. The average increase in the FI among those without cognitive impairment was 3% per year ( $r = 0.91$ ;  $p < 0.001$ ). The FI was proposed as a sensitive predictor of survival due to inclusion of novel frailty deficits not found in most frailty assessments and its ability to plot a mortality trajectory.

In a study of community older adults ( $N = 2,914$ ,  $\geq 65$  years), a Frailty Index (FI) included 20 deficits derived from the clinical exam ( vision loss, hearing loss, impaired mobility, vascular problems, abnormal gait, impaired vibration sense, abnormal limb tone, difficulty with cooking, bathing, toileting, going out, grooming, skin, urinary, gastrointestinal problems, diabetes, hypertension) (Mitnitski, Mogilner, MacKnight, & Rockwood, 2002). Deficits were summed and computed to represent a proportion of the total possible number of deficits. The FI projected a linear relationship with mortality. Annually, women accumulated more deficits, were more frail, but had lower mortality risk compared to men of the same age. The FI identified gender differences in health status and frailty trajectories.

In a cross sectional population-based study ( $N = 26,712$ ), which FI consisted of 32 deficits (ADL, IADL, diseases, symptoms, self-rated health), was used to determine if frail persons have more health problems than nonfrail counterparts (Kulminski et al., 2007). Comparisons of cohorts found that the FI characterized age-associated processes and predicted mortality better than chronological age. At younger ages, deficits accrue more slowly, but accelerate with age, and at very old ages, deficits in some decelerated.

Rockwood and colleagues (2011) examined frailty in community adults ( $N = 14,127$ , range, age 15-102 years, 14-year follow-up) using a 42-deficit FI (symptoms, disabilities, ADLs, IADLs, diseases, self-rated health). Frailty level was determined by summing the number of deficits and dividing by the total number of deficits (42). The score was assigned to one of four categories: relatively fit, less fit, least fit, or frail. At baseline, 50.8% were relatively fit and 7.2% were frail. At subsequent two-year follow-up, the mean FI value increased exponentially. Frailty prevalence was linearly associated with age. In the 15-30 year old age group, the FI was 2%, in the  $\geq 65$  year age group, the FI was 22.4%, and in those  $\geq 85$  years, the FI was 43.7%. The relatively fit at baseline tended to remain healthy, while those who were less fit or more frail were more likely to worsen or die. About 25% fluctuated between fitness and frailty. Fitness declined with age and the less fit were unlikely to increase level of fitness.

In another iteration of the deficit accumulation framework, Rockwood et al. (2005) examined the construct and predictive validity of the Clinical Frailty Scale (CFS) in the CSHA ( $N = 2,305$ ) based on 70 deficits (ADL, IADL, physical and cognitive function, chronic diseases, neurological problems, geriatric syndromes, signs and

symptoms). Physician clinical judgment classified frailty into 7 categories, where 1 = Very fit (robust, active, energetic, motivated); 2 = Well (no active disease but less fit); 3 = Well (with treated comorbid disease, disease symptoms well controlled); 4 = Apparently vulnerable (not frankly dependent, but “slowed up” and have disease symptoms); 5 = Mildly frail (limited IADL dependence); 6 = Moderately frail (need ADL and IADL assistance); and 7 = Severely frail (completely dependent on others or terminally ill) (Rockwood et al., 2005, p.490). Those with greater deficit accumulation and higher CFS scores tended to be older, female, cognitively and mobility impaired, and had more comorbid illness. Only 21% were Very fit or Well whereas 30% were Moderately or Severely frail. The CFS scores were compared with two other frailty indexes. The CFS had good criterion validity with a dose-response effect for 5-year mortality and institutionalization and acceptable construct validity, where worse health indicators and greater numbers of deficits were associated with severe frailty.

In secondary analysis of data from the second Canadian Study of Health and Aging (CSHA-II), a FI based on comprehensive geriatric assessment (CGA) was performed in clinics, nursing homes, and patients’ homes ( $N = 2,305$ , five-year follow-up; Jones et al., 2005). The FI-CGA consisted of 10 impairment domains and performance measures. The proportion of deficits accumulated in each domain was computed to derive a score which correlated with 7 levels of fitness and frailty (as described above, Rockwood et al., 2005). Higher level of frailty was associated with older age, less education, and female gender. The FI-CGA correlated highly with other validated frailty indexes ( $r = 0.76$ ). Frailty was significantly associated with mortality

( $HR = 1.23$ ; 95%  $CI$ , 1.18–1.29) and institutionalization ( $HR = 1.20$ ; 95%  $CI$ , 1.10–1.32), in adjusted models for age, sex, education. The FI-CGA demonstrated a dose response where more deficits were associated with worse frailty and increased health and social service utilization.

The deficit accumulation framework was examined in two hospital-based studies. Hastings and colleagues (2008) conducted a secondary analysis of data from the Medicare Current Beneficiary Survey ( $N = 1,851$ ) of patients discharged from the emergency department and examined adverse outcomes including repeat ED visits, hospital admission, nursing home discharge, or mortality within 30 days of the ED visit. Older adults presenting to the ED with the highest number of deficits had the shortest time to first adverse outcome, higher risk for adverse outcomes ( $HR = 1.44$ ; 95%  $CI$ , 1.06–1.96) and serious adverse outcomes (hospitalization, nursing home admission, mortality;  $HR = 1.98$ ; 95%  $CI$ , 1.29–3.05). There was no association between level of frailty and repeat ED visit within 30 days.

In a retrospective study of hospitalized older adults admitted to a tertiary care academic hospital and underwent abdominal surgery ( $N = 102$ ,  $\geq 65$  years, mean age, 72 years), neither the deficit accumulation index (DAI) of 39 variables nor the ASA (American Society of Anesthesia) class  $> 3$  predicted post-operative complications (R. Cohen et al., 2012). The Braden Scale score, a validated measure of pressure ulcer risk, was the only independent predictor of post-operative complications; only length of stay was statistically significant.

### **Multidimensional Frailty Assessment**

An increasing number of research studies address biopsychosocial aspects of frailty. Medical problems and clinical decision-making can be complex due to heterogeneous combinations of sociodemographic, biological, psychological, social, behavioral, spiritual, environmental factors. Pathogenic processes such as inflammation and stress confound demarcations between aging, disease, disability, and frailty. Research is needed to examine individual differences in biopsychosocial factors, life circumstances and stressors, disease and symptom burden, and physiologic indicators of frailty (Stephoe et al., 2007).

In a study of the integral conceptual model of frailty in community-living older adults ( $n = 213, \geq 75$  years; Gobbens, van Assen, Luijkx, & Schols, 2011), relationships between life-course determinants, morbidity, and three domains of frailty (physical, psychological, social) and their effects on adverse outcomes were examined (Gobbens et al., 2011). Life-course determinants, morbidity, and frailty combined accounted for 26-57% of variance in outcomes. The effect of morbidity on adverse outcomes was partly mediated by frailty, but not life-course determinants. Adverse outcomes were associated with physical, psychological, social domains of frailty, life-course determinants, and morbidity, supporting a multidimensional approach to frailty.

In a study of outpatient chemotherapy patients ( $N = 50, \geq 70$  years), multidimensional frailty assessment was used to determine if this approach better predicted treatment tolerance than traditional oncology risk assessment that included age, health status, ADL, and IADL function (Retornaz, Potard, Molines, & Rousseau, 2011).

At baseline, participants were older and in good health with high ADL and IADL function. A 7-item frailty assessment (nutrition, mobility, strength, energy level, physical activity, mood, cognition) and assessment of ADL and IADL disability classified four groups: (a) no frailty criteria, IADL, or ADL disability; (b) frailty criteria without IADL or ADL disability; (c) IADL disability without ADL disability; and (d) ADL disability only. In this cohort, 42% were frail without ADL or IADL disability, 12% had no frailty criteria, and 16% had ADL disability only. Over two-thirds (68%) had more than two frailty markers. Frailty assessment identified more patients at risk for adverse effects from chemotherapy than the traditional risk assessment.

The Edmonton Frail Scale (EFS) consists of 10 domains (17 items): general health status (hospitalization in past year, self-rated health), cognition (clock-drawing test), functional independence (IADL function), social support (available person for assistance), medication use ( $\geq 5$  routine medications, forget to take medications), nutrition (weight loss), mood (self-reported sadness or depression), continence (uncontrolled loss of urine), functional performance (three-meter Timed Up-and-Go test; Rolfson et al., 1999). Frailty items were rated on a three-point scale and summed. A higher score suggested more severe frailty. In a study of surgical patients ( $N = 125$ ,  $\geq 70$  years), a score  $> 3$  on the EFS was predictive of frailty, post-operative complications, increased length of stay, and inability to be discharged home, independent of age (Dasgupta et al., 2009). In a sample of older adult inpatients and outpatients ( $N = 158$ ), the EFS was compared to the Geriatrician's Clinical Impression of Frailty (GCIF;

Rolfson et al., 1999). Scoring ranges from 0 (no frailty) to 5 (maximal level of frailty). The EFS significantly correlated with the GCIF and demonstrated validity and reliability.

In a population-based study of older adults ( $N = 1,007$ ,  $\geq 65$  years, four-year follow-up), Ravaglia et al. (2008) developed a frailty index based on self-report and standardized measures for 17 predictors. Statistical analyses identified nine independent mortality predictors for frailty:  $\geq 80$  years, male, low physical activity, sensory deficits, calf circumference  $\leq 31$  cm, IADL dependence, gait and performance score  $< 24$ , and pessimism about one's health. Results indicated that a one-point increase in the frailty score doubled the risk for fractures, new or worsening ADL disability, hospitalization, and mortality.

Balducci and Stanta (2000) developed a frailty instrument to differentiate persons with cancer and tolerance of oncology treatments. Frailty criteria were  $\geq 85$  years, dependence in  $\geq 1$  ADL, comorbidity (serious cardiovascular, respiratory, cerebrovascular disease  $\geq$  diseases, or comorbidity index), one or more geriatric syndromes (moderate dementia,  $\geq 3$  falls in one month, delirium [due to pulmonary or urinary tract infection, coronary ischemia, drugs], urinary and/or fecal incontinence, osteoporotic fractures, failure-to-thrive, and neglect and abuse. A greater number of problems indicated more severe frailty, however, the investigators noted that some criteria may merit greater weighting in the scoring algorithm. For example, osteoporosis and incontinence may not have the same "ominous significance" as failure-to-thrive (Balducci & Stanta, 2000, p. 247). This was the only frailty instrument to include failure-to-thrive in its operational definition. Age was qualified as a marker of potential

vulnerability which contrasts with inherent factors related to resilience where longevity is not inevitably linked to decline and frailty.

The Frailty Staging System (FSS) is a screening tool developed for use in general practice to assess severity of functional impairment in domains often overlooked in routine physical assessment in older adults (Lachs et al., 1990). The FSS assesses vision, hearing, mental status, upper and lower limb function, urinary incontinence, ADL, IADL, environmental hazards, and social support. Scoring is based on the presence or absence of the function (0, 1) where a score of 1 triggers comprehensive assessment of that domain. The FSS does not stratify level of frailty.

In a randomized control study to assess mortality in older adults with heart failure ( $N = 120$  with heart failure,  $N = 1,139$  without heart failure,  $\geq 75$  years, 12-year follow-up), Cacciatore et al. (2005) modified the FSS to define levels of frailty. The modified FSS addresses seven domains: disability (ADL), mobility (heavy housework, walk up and down stairs, walk half a mile), cognition (MMSE  $< 24$ ), vision (4 = no problem, 1 = blindness), hearing (4 = no problem, 1 = total deafness), urinary incontinence (total incontinence), and social support (4 = high support, 1 = lowest support). Each domain is scored dichotomously and summed. Frailty is categorized into 3 classes based on the sum score: Class 1 (0–1 point), Class 2 (2–3 points), Class 3 (4–7 points). Other covariates were number of medications, comorbidity, cardiac medications, blood pressure, heart rate, and the New York Heart Association (NYHA) functional classification system. Prevalence of Class 3 frailty (FSS score 4 to 7, where 7 is most severe level) in those with heart failure was 15% compared to 5% without heart failure. Frail heart failure patients were

significantly older, prescribed more medications, had poorer cognitive function, more medical problems, greater ADL disability, and lower survival compared to Class 1 (FSS score 0–1). In those with heart failure, frailty and the NYHA were not significantly correlated. Frailty was a better predictor of mortality than NYHA. None of those with Class 3 frailty survived after nine-year follow-up whereas all of those in NYHA Class IV, the most functionally limited group, did. The proportion of frail patients with ADL disability was 83% compared to 25% of NYHA Class IV patients. Mortality rates were significantly higher among the frail heart failure group in all classes of frailty in regression analyses compared to the non-heart failure group, after adjusting for covariates. The modified FSS determined that frailty represented a new independent variable for mortality prediction in heart failure. However, the FSS makes distinctions between frailty and ADL impairment difficult to determine.

In the Cooperative Cardiovascular Project, a modified FSS was used to define frailty in patients who experienced acute myocardial infarction (AMI;  $N = 43,370$ ,  $\geq 65$  years) to determine the rate of beta blocker prescription (Vitagliano et al., 2004). The modified FSS assessed functional impairment in only three domains: cognition, mobility, and urinary continence. Cognitive impairment was defined by the diagnoses of dementia, Alzheimer's disease, chronic confusion, organic brain syndrome, chronic brain syndrome, deteriorating mental status, and senility; delirium was classified as no impairment. Mobility impairment was defined as ability to walk or unable to walk (or needs a cane, prosthesis, brace, assistance device, or crutches, or non-ambulatory). Urinary incontinence was defined as continent or incontinent (totally or occasionally). The

modified FSS score was the sum of impairments that were rated according to four levels of severity. Frailty Stage I classified no impairment. Frailty Stages II, III, and IV classified impairments in one, two, or all three domains (Vitagliano et al., 2004). The prevalence of frailty with AMI in Stage 1 was 80% (not frail), Stage II, 16%, Stage III, 3%, and Stage IV, 1%. Those prescribed a beta-blocker were 21% less likely to die within one year (relative risk ( $RR$ ) = 0.79,  $p$  = 0.0001). Similar survival was reported in those with and without functional impairments thus beta blocker therapy provided a survival benefit at all levels of frailty.

Preclinical disability, functional decline, and ADL disability in community older adult populations is relevant to frailty. In the WHAS II ( $N=436$ , 70-80 years, community-living women, least disabled, 18-month follow-up) a preclinical stage of physical function decline preceded onset of disability (Fried, Young, Rubin, Bandeen-Roche, & WHAS II Collaborative Research Group, 2001). Standardized measures of function and disease state were obtained (gait speed, chair stands, handgrip and hip flexor strength, balance, spirometry, visual function, treadmill, others). At follow-up, decreased physical performance and increased disease frequency was associated with self-reported decline in mobility function. Study findings suggest that different levels of disease severity, impairment, and physical performance were associated with different levels of self-reported function. Identifying early stages of functional decline may improve detection of older adults at risk of becoming disabled or who are frail.

Attention to functional decline and ADL disability is particularly important in hospitalized adults since these conditions are recognized as adverse outcomes of frailty.

At its earliest inception, frailty is hypothesized to precede functional decline and ADL disability (Fried, Tangen, et al., 2001; Fried et al., 2004). However, there is considerable overlap between frailty and functional decline, disability, and morbidity, where boundaries are less distinct as a function of time and the interactions among these. For example, the etiology and trajectory of functional decline and ADL disability are influenced by stressors associated with hospitalization and care delivery processes (Boltz et al., 2012; Boyd et al., 2005; C. J. Brown et al., 2004; C. J. Brown et al., 2009).

Precursors or risk factors for functional decline and ADL disability may have linkages to frailty through their impact on biologic processes that impact multiple body systems that exert cumulative adverse effects over time. Frailty may also develop without evidence of functional decline, ADL disability, or illness but the underlying physiologic vulnerability is associated with poor response to stressors and recovery, thus functional decline and disability may manifest under acute clinical circumstances and rapidly progress.

In a systematic review of 28 prospective, longitudinal studies, the predictive value of frailty indicators on ADL disability was assessed in community-living older adults (Vermeulen, Neyens, van Rossum, Spreuwenberg, & de Witte, 2011). Although there was variability in the definition and measurement of ADL function and disability indicators and data could not be pooled, study findings indicate that weight loss, gait speed, grip strength, physical activity, balance, and lower extremity function predicted future ADL disability. Slow gait speed and low physical activity were the strongest predictors. Study findings suggest that assessing and monitoring physical function may help identify older adults who could benefit from mobility-enhancing interventions.

Several tools screen for frailty using a functional inventory then follow-up with frailty assessment using CGA. For example, The Vulnerable Elders Survey (VES-13) is a 13-item assessment a function-based tool developed by the Rand Corporation that identifies older people at risk for physical function decline and death (Saliba et al., 2001). The VES-13 is a survey tool that includes self-rated health and ADL and IADL function. In a nationally representative community-based survey ( $N = 2,205$ ,  $\geq 65$  years, Medicare beneficiaries), a VES-13 score  $\geq 3$  identified 32% as vulnerable. The vulnerable group had 4.2 times the risk of death or functional decline over two-years compared to those with scores  $< 3$  ( $AUC = 0.78$ ). The addition of self-reported diagnoses did not improve the predictive ability of this tool. In a longitudinal study of community-living older adults in two managed care organizations identified as having moderate to high risk of death and functional decline defined by a VES-13 score  $\geq 3$  at baseline ( $N = 420$ ,  $\geq 65$  years, mean follow-up, 11 months), VES-13 scores significantly predicted death and functional decline ( $AUC = 0.66$ ; Min, Elliott, Wenger, & Saliba, 2006). The risk of death and functional decline increased from 23% among those with VES-13 scores of 3- 60% among those with a score of 10. As demonstrated in the prior study, gender and morbidity were not significant predictors. The VES-13 is a useful screening tool to detect risk of health deterioration in a vulnerable older population. Several studies report the use of the VES-13 as part of a two-step screening process to identify high risk individuals who would benefit from a full CGA and maximize efficiency and case-finding (Molina-Garrido & Guillen-Ponce, 2010).

To facilitate case-finding and screening in primary care the FRAIL Scale was developed by an international advisory panel (Abellan van Kan, Rolland, Bergman, et al., 2008). The FRAIL Scale identifies older adults at risk for health decline, dependency, and poor outcomes in a short, practical instrument. FRAIL is an acronym for: (a) Fatigue; (b) Resistance (climb stairs); (c) Ambulation (walk a standardized distance); (d) Illnesses (number); and (e) Loss of weight ( $\geq 5\%$ ). A maximum score of 48 indicates severe frailty. Psychometric or clinical data were not reported. This instrument has gained recognition as a practical and clinically relevant tool for frailty screening assessment that should be adopted by clinicians across clinical care settings (Heuberger, 2011).

### **Comprehensive Geriatric Assessment (CGA)**

Comprehensive geriatric assessment (CGA), a cornerstone in geriatric practice is an interdisciplinary diagnostic and treatment process that determines the older adult's multidimensional medical, psychosocial, and functional abilities and needs to develop a coordinated care plan, referral to health and social services, and planned follow-up (Wieland & Hirth, 2003). CGA provides a multidimensional view of BPSS health status based on interprofessional geriatric expertise that identifies deficits in BPSS function and risk factors for frailty before objective manifestations occur (Gobbens et al., 2010b, 2010c, 2011; Whitson et al., 2007).

The Clinical Global Impression of Change in Physical Frailty (CGIC-PF) (Studenski et al., 2004) was designed from survey and interview data from experts in frailty, geriatric clinicians, and elderly patients and caregivers. The CGIC-PF consists of six assessment domains (mobility, balance, strength, endurance, nutrition, neuromotor

performance) and seven domains for consequences (medical complexity, healthcare utilization, appearance, self-perceived health, ADLs, emotional status, social status). Each domain has two to four indicators rated on a seven-point scale which are scored and summed (Markedly worse Markedly improved). Frailty level was rated from seven (best) to zero (worst). At subsequent visits, a rating scale was used to record changes. The CGIC-PF has not been validated, but the investigators recommended that the tool be used in clinical practice to monitor frailty status, interventions, and outcomes.

The CGA is a promising approach for use in hospital settings because it addresses frailty as a multidimensional syndrome, is clinically relevant, and can identify specific needs and interventions for individuals (Gobbens et al., 2010b, 2011; Jarrett et al., 1995; Rønning et al., 2010; Studenski et al., 2004; Wieland & Hirth, 2003). Limitations of CGA are that there is (a) no standardized approach to assessment of each domain; (b) reliance on subjective clinician judgment or patient self-report; (c) variability in protocols used for performance measures; (d) lack of evaluation methods to determine reliability and validity of CGA assessment tools; and (e) lack of normed cut-points for frailty (Chalcraft, 2010; Studenski et al., 2004). CGA requires geriatric expertise, trained staff, extra time, adequate space, and a high functioning interdisciplinary team.

### **Physical Performance Measures**

Tests of physical performance as an indicator of intact integrated body system function and risk for physical function decline. Tests of mobility, balance, and muscle strength have been used alone or as part of frailty assessment. In a prospective cohort study ( $N = 487, \geq 65$  years), Studenski et al. (2011) found that the Short Physical

Performance Battery (gait speed, chair stands, standing tandem balance) were independent predictors of 12-month hospitalization and health and functional decline.

Performance measures such as gait speed, timed chair stands, balance tests, and handgrip strength, may improve precision in detecting frailty since task performance reflects integration of many physiologic functions (Purser et al., 2006). Performance tests require intact and coordinated function, musculoskeletal strength, balance, and endurance, which require intact brain, spinal cord, peripheral nerves, heart and lung function (Studenski, 2009).

In a systematic review, slow gait speed was a consistent risk factor for frailty, disability, cognitive impairment, institutionalization, falls, and mortality (Abellan van Kan et al., 2009). Gait speed is an important independent predictor of frailty, morbidity, physical function impairment, falls, and mortality (Abellan van Kan et al., 2009; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Hardy, Perera, Roumani, Chandler, & Studenski, 2007; Montero-Odasso et al., 2011; Purser et al., 2005, 2006; Studenski et al., 2011; van Iersel & Rukkert, 2006; Verghese & Xue, 2011). Studenski (2009) noted that slowed movement is a universal age-related biological process reflecting decline in physiologic vitality and the integrated performance of numerous organ systems. Gait speed may serve as a central, core indicator of health and function. Walking requires body support, neurocognitive and neuromuscular processes about timing, positioning, stance, cadence, and stride length that is influenced by muscle strength, balance, and power, and cardiorespiratory fitness. The simultaneous interactive functioning of multiple organ systems may provide an estimation of fitness, disease and symptom burden, and

the energy expenditure required to meet ADL and self-care needs and daily demands requiring varying degrees of energy expenditure (Studenski, 2009). In one study, gait speed was significantly associated with self-reported limitations in three home-based activities (walking inside the home, climbing up and down stairs; Verghese, Wang, & Holtzer, 2011).

In a study of acutely ill hospitalized older veterans admitted to a geriatric evaluation and management (GEM) unit, gait speed was used as an indicator of health and functional status ( $N = 1,388$ , age 74.2, 98% male, one-year follow-up; Purser et al., 2005). Study findings reported that slower baseline walking speed (e.g., for each reduction of .10 meters/second in walking speed) was associated with poorer health status, poorer physical functioning, more disabilities, additional rehabilitation visits, increased medical-surgical visits, longer length of stay, and higher costs ( $M = \$1,334$ , range, \$869 to \$1,798). In contrast, each .10 m/s per year increase in walking speed resulted in improved health status and physical function, fewer ADL and IADL disabilities, shorter length of hospital stay, and one-year cost reductions of \$1,188 on average. In this study, gait speed was clinically relevant and feasible in assessment of acutely ill, hospitalized older adults. Repeated measurement over time would provide objective data on health status that may aid in identifying latent functional decline and guide interventions that prevent steady decline and future dependence as well as identify those who may be more likely to need supportive health and social services in order to minimize health care costs and reduce hospitalization.

In a study of older adults ( $N = 333, \geq 70$  years), higher serum IL-6 levels were significantly associated with slower gait speed (adjusted for age, gender, education, morbidity) where a one-unit increase in baseline log IL-6 level was associated with a 0.98 cm/s faster gait speed decline per year ( $p = 0.002$ ; Verghese, Holtzer, et al., 2011). IL-6 has catabolic effects on muscle which contributes to muscle weakness and slow gait speed. In a study of community-living older adults ( $N = 1,858, \geq 45$  years, Johnston County Osteoarthritis Project), faster gait speed (normal walking speed over 8 feet) was associated with lower incidence of radiographic and symptomatic knee osteoarthritis (Purser et al., 2012). Slower gait speed may be an early indicator of osteoarthritis, with implications for frailty since joint stiffness and pain negatively impacts physical activity. Clinically-confirmed osteoarthritis at a younger age increases risk for chronic pain, impaired mobility, ADL dysfunction, and frailty (K. Covinsky, 2006).

Gait speed has been suggested as a vital sign for functional capacity for independent living, risk for disability, and as a screening tool to plan care and predict adverse health outcomes (Abellan van Kan et al., 2009; Cesari, 2011a; Cesari et al., 2009; Ferrucci et al., 2000; Studenski, 2009). Gait speed has implications for independent functioning and is predictive of important outcomes. Determining if a person's walking speed is abnormal requires normed values for comparison.

In a recent meta-analysis of 41 articles to describe normal gait speed for healthy adults ( $N = 23,111, 40-99$  years, walk at normal pace for 3 to 30 meters) stratified by age and gender (Bohannon & Williams Andrews, 2011), gait speed was homogeneous within age groups, ranging from a mean of 143.4 cm/second (14.3m/s) for men aged 40 to 49

years to a mean of 94.3 cm/second (9.43m/s) for women aged 80 to 99 years. For older adults, studies have reported gait speed cutpoints of 1m/second (Afilalo et al., 2012) and 0.65 m/s (Purser et al., 2005). In a study of medical and surgical cardiac surgery patients, gait speed was a significant independent predictor of frailty and major morbidity and mortality (Afilalo et al., 2010; Purser et al., 2006). In a study of acutely ill, hospitalized, older male veterans ( $n = 1,388$ , 74.2 years, one-year follow-up; Purser et al., 2005) walking speed predicted health status and hospital costs. Each 0.10 m/s reduction in baseline walking speed was significantly associated with worse health status, poorer physical function, more disabilities, additional rehabilitation and medical-surgical visits, longer hospital stay, and higher costs that averaged \$1,334. Alternatively, each 0.10 m/s/year increase in walking speed resulted in improved health status and physical function, fewer basic and instrumental disabilities, fewer hospitalization days, and one-year cost reductions of about \$1,188.00. Gait speed is useful in the assessment of acutely ill, hospitalized older adults and may help predict those who will need and use more health-related services (Purser et al., 2005). Normed data from large samples of middle-aged and older adults can provide guidance for interpretation of gait speed in clinical practice however standardized procedures must be considered, such as distance for acceleration and deceleration, measured walking distance, whether a turn involved).

**Other physical performance measures.** Physical performance measures including tests for balance, pulmonary function, handgrip strength, repeated chair stands, are significantly associated with functional decline, falls, and frailty (Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Guralnik & Ferrucci, 2003; Klein, Klein, et al.,

2003; Speechley & Tinetti, 1991). Chin A Paw et al. (2003) compared three definitions of frailty ( $N = 450$  men  $\geq 65$  years, three-year follow-up, Zutphen Elderly Study) identified as inactivity plus low energy intake; inactivity plus weight loss; and inactivity plus low BMI. The combination of inactivity plus weight loss was the strongest predictor of mortality and functional decline. The group defined by inactivity plus weight loss also had poor grip strength, slow gait speed, and increased disability compared to those who were active with normal BMI.

Data from the MacArthur Studies of Successful Aging ( $n = 880$ , subset of high-functioning older adults [ $n = 1189$ ]) and the Established Populations for Epidemiologic Studies of the Elderly (PEESE; subset,  $n = 4030$ ) indicated that poor physical performance in handgrip strength, chair stands, and six-minute walk time were associated with serum CRP and IL-6 levels (Taaffe et al., 2000). Faster walking speed was significantly associated with lower IL-6 and lower CRP in adjusted models (age, gender, race, BMI, smoking, nonsteroidal anti-inflammatory drugs, morbidity). Lower CRP level was significantly associated with high grip strength. There were no significant differences for chair stands. Performance measures at seven-year follow-up declined significantly for grip strength (18%), walking speed (31%), but not chair stands. Baseline IL-6 and CRP were not associated with a change in performance. Those unable to undergo testing or who died had significantly higher baseline IL-6 and CRP levels and slower walking speed. CRP and IL-6 levels did not predict change in physical performance which is potentially explained by the high-functioning, physically active older adult sample, since physical activity reduces level of inflammatory biomarkers.

Runge and Hunter (2006) assert that physical performance tests are essential in frailty assessment. Suggested tests include: (a) Gait velocity, which was identified as the single best measure of gait stability and predictor of adverse events; (b) Five timed chair rises to assess risk for falls and injury; (c) Tandem standing and walking to measure balance; (d) Timed Up & Go Test as a global screening procedure; (e) Clinical gait analysis; and (f) Mechanography to analyze kinetics during a two-legged jump (Runge & Hunter, 2006). In a study investigating the added value of performance tests in predicting adverse events in older adults, although gait speed has been validated as the most significant predictor, other tests such as repeated chair stands and balance tests are equally prognostic and are acceptable substitutes (M. Brown, Sinacore, Binder, & Kohrt, 2000; Cesari et al., 2009; Purser et al., 2005, 2006; Puts et al., 2005; Theou, Jones, Jakobi, Mitnitski, & Vandervoort, 2011).

Research is needed on performance tests in acutely ill hospitalized adults. Guidelines are needed for types of tests appropriate for this population or sub-groups, standardized protocols, frequency and timing of administration, methodologies for scoring and normed scales for interpretation of results, dedicated time for staff training and time for integrating performance testing in clinical care, patient inclusion and exclusion criteria, and safety factors based on risk profiles. Performance tests are more easily administered in community settings, but the feasibility of administering performance tests on busy clinical units in acutely ill hospitalized adults requires further research. Given the heterogeneity of the aging population, norms for frailty assessment measures are needed since there is little guidance on cutpoints for performance tests

performed in acutely ill hospitalized adults that accurately represents health status and risk for or level of frailty. Reexamination of referent categories of performance and laboratory tests for what constitutes “within normal limits” and “abnormal” in frailty assessment is needed (Heuberger, 2011).

### **Concordance of Frailty Definitions and Prevalence**

Given substantial diversity in frailty definitions, it is not surprising that there is poor concordance in frailty prevalence across research studies. In cross-study comparisons, only a small% of the sample is classified as frail by different assessment tools. For example, van Iersel and Rukkert (2006) compared frailty criteria for two frailty assessment frameworks and two performance measures (gait speed, handgrip strength) in an acute care geriatrics ward ( $N = 125$ ) to evaluate concordance and determine the validity and ranking of individual predictors. The first framework was based on an index of accumulation of deficits and included cognitive decline, ADL disabilities and urinary incontinence (Rockwood et al., 1999). The second framework was defined as the cycle of physical frailty using the Fried Frailty Index (Fried, Tangen, et al., 2001). The prevalence of frailty defined by individual criteria or the two frameworks varied markedly. Gait speed classified 88.8% as frail, compared to 62.4% for the CHS cycle of frailty framework, 48% for the accumulated deficit framework, and 36% for handgrip strength (van Iersel & Rukkert, 2006).

In the Health and Retirement Study (HRS;  $N = 11,113$ ,  $\geq 65$  years), Cigolle et al. (2009) compared three definitions of frailty: Functional Domains model (16 variables for nutrition, cognitive, physical, sensory function; Strawbridge et al., 1998, Alameda

County Study [ACS]), Biologic Syndrome model (five criteria: weight loss, exhaustion/fatigue, weakness, gait speed, physical activity; Fried, Tangen, et al., 2001, Cardiovascular Health Study [CHS]), and Burden model of accumulated deficits (Functional Index, 38 items from a 70-item scale for categories of symptoms, diseases, neurological conditions, cognition, mood, mobility, function (Rockwood, Andrew, & Mitnitski, 2007; The Canadian Study of Health and Aging [CSHA], 2001). Separate analyses were conducted using these tools in different study sub-populations. In the first analysis, the prevalence of frailty was compared in the HRS population based on the sample characteristics of the populations in which each of the three frailty models were originally tested ( $n = 1,657$ ). For the Functional Domains model, the HRS frailty prevalence was 29% compared to 26% for the ACS. For the Biologic Syndrome Model, the HRS frailty prevalence was 11% compared to 7% for the CHS. For the Burden model, the HRS frailty prevalence was 32%, however, the CSHA does not compute prevalence, but estimates proportionate risk levels for frailty by age relative to mortality based on deficit accumulation.

In the next set of analyses where the models were compared to each other in the HRS population, 30.2% were frail according to at least one framework. The Biologic Syndrome model classified 10.9% as frail, the Functional Domains model, 20.3%, and the Burden model, 15.4%. Only 3.1% were classified as frail by all three models. In a final analysis, sociodemographic and other characteristics of the HRS sample were considered. The Functional Domains model showed the least overlap with other models; the Biologic model classified 76.1% as frail and the Burden model classified 72.1% as

frail. Given the lack of concordance, each model may characterize different but overlapping aspects of frailty.

Kiely, Cupples, and Lipsitz (2009) compared two frailty assessments in community older adults ( $N = 765$ ), the Study of Osteoporotic Fractures (SOF) Index (weight loss, inability to rise from a chair five times without using the arms, reduced energy level) and the Fried Frailty Index (Fried, Tangen, et al., 2001). The SOF Index classified 4.2% as frail whereas the Fried Frailty Index classified 10% as frail. Both instruments similarly predicted falls, hospitalization, emergency department visits and disability according to level of frailty. Despite dissimilar prevalence rates, the shorter SOF Index was judged favorably since it similarly predicted poor outcomes and was easier to use in practice.

Two frailty definitions were compared in the Canadian Study of Health and Aging (CSHA;  $N = 2,305$ ,  $\geq 70$  years) to test convergent validity with each other and other health status measures (Rockwood et al., 2007). The frailty phenotype was operationalized by modified CHS Frailty criteria (timed-up-and-go test substituted for gait speed frailty criteria, low physical activity criteria operationalized as self-report of needing assistance to walk or unable to walk versus the CHS physical activity questionnaire, exhaustion criteria operationalized by self-report of “tired all the time,” weakness criteria was directly assessed on physical exam; other factors pertinent to the CHS criteria were obtained from the physical exam to provide convergent validity (e.g., test of functional reach, observation of irregular gait pattern). The Frailty Index (FI) was operationalized by 70 deficits identified from the clinical exam that included diseases,

ADL, signs and symptoms, neurological findings, mobility, and cognition. The frailty phenotype and FI demonstrated moderate correlation with each other ( $R = 0.65$ ) and with measures of function but less well with cognition. Each indicator from the frailty phenotype was associated with impairment in Functional Reach. Analysis of the FI does not differentiate frail from nonfrail but uses a cut point of 0.25 based on the sum of the deficits divided by the number of deficits in the index (70) which corresponds to the crossing point of the robust and prefrail group. Because the CHS criteria for the frailty phenotype were not exactly reproduced, various calculations were done to determine which variables best defined frailty. When comparing the CHS frailty criteria with the FI deficits, the frailty phenotype was not as influential as the number of deficits present for the FI; there were no significant differences in the distribution of deficits or criteria. Both frailty definitions differentiated levels of frailty by severity, and a higher level of frailty was associated with more adverse outcomes. The FI does not assume independence of the frailty criteria or validate frailty as a clinical syndrome composed of distinct elements. The dose-response in the FI deficit accumulation and poor outcomes suggests that the FI may characterize different subtypes or aspects of frailty.

In another study, the physical frailty phenotype (CHS Frailty criteria-named Composite A), an index of accumulated deficits (named Composite B), and two performance tests (gait speed, grip strength) were compared in their ability to predict 6-month mortality in hospitalized older adults with minimum two-vessel coronary artery disease who were scheduled for cardiac catheterization ( $N = 309$ ,  $\geq 70$  years) (Purser et al., 2006). Frailty prevalence was 27% by Composite A and 63% by Composite B. Slow

gait speed and poor grip strength were stronger predictors of six-month mortality than either composite score, as follows: gait speed ( $OR = 3.8$ ; 95%  $CI$ , 1.1–13.1), grip strength ( $OR = 2.7$ ; 95%  $CI$ , 0.7–10.0), Composite A ( $OR = 1.9$ ; 95%  $CI = 0.60$ –6.1), chair-stands ( $OR = 1.5$ ; 95%  $CI$ , 0.5–5.1), Composite B ( $OR = 1.3$ ; 95%  $CI$ , 0.3–5.2).

In a prospective population-based study, the Frailty Index (FI; 43 items) and the Conselice Study of Brain Aging Score (CSBAS; seven items) were compared in a rural community-living older adults ( $N = 1,016$ ,  $\geq 65$  years, four-year follow-up, Italy; Lucicesare, Hubbard, Searle, & Rockwood, 2009). The FI (based on the deficit accumulation framework) included signs, symptoms, diseases, disabilities, and abnormal laboratory measures derived from comprehensive geriatric assessment. The CSBAS (modified from the nine-item Easy Prognostic Score developed by Ravaglia et al. (2008) includes physical activity, gait, balance, sensory deficits, medications, IADLs, calf circumference, self-rated health. In analyses, frailty was assessed along an age trajectory and gender was not a significant predictor of mortality based on prior CSBAS research and was not included in the frailty indexes. FI scores are computed mathematically as a plot of variables with scores that range from 0 to 1, where a value of 0.25 is the cut point for a “clinically important level of frailty” (Lucicesare et al., 2009, p. 279). Higher scores indicate more severe frailty. The CSBAS score was a sum of variables that range from 0 to 7. Both measures predicted frailty and correlated well with each other ( $r = .72$ ,  $p < 0.001$ ). Frailty was independently predictive of mortality better than age (FI,  $HR = 5.26$ ; 95%  $CI$ , 1.05–26.42,  $p < 0.040$ ; CSBAS,  $HR = 1.52$ ; 95%  $CI$ , 1.28–1.81,  $p < 0.001$ ).

Two screening tools, the Barber Questionnaire (BQ) and the Vulnerable Elderly Survey (VES-13) were studied in older women diagnosed with early breast cancer ( $N=41$ ,  $\geq 65$  years, outpatient care) and compared to CGA (Molina-Garrido & Guillen-Ponce, 2010). The BQ is a nine-item tool that was originally developed to identify older persons at risk for dependence. The VES-13 is a 13-item tool that assesses age, self-perceived health status, ADL and physical fitness, and IADL function. A score  $> 0$  on the BQ or  $\geq 3$  on the VES-13 indicated the need for CGA. The CGA included the Barthel Index, Lawton-Brody IADL scale, Charlson Comorbidity Index, NSI nutritional screen, medications, Pfeiffer Short Portable Mental Status Questionnaire, and the modified Gijon social scale. Deficits in any domain were attributed one point for the domain, and a sum  $\geq 2$  points for the CGA indicated increased risk for frailty. The BQ and VES-13 were compared with the CGA. The risk of frailty was 41.76%, 29.3% and 55.7% when evaluated with the BQ, VES-13 and CGA, respectively. The correlation between the BQ and CGA was fair ( $ICC = 0.672$ ), but the correlation between the VES-13 and CGA was very good ( $ICC = 0.814$ ). Prediction of frailty risk was intermediate ( $AUC=0.719$ ) for the BQ and high ( $AUC = 0.876$ ) for the VES-13. The use of the VES-13 followed by CGA for VES-13 scores  $\geq 3$  for screening was recommended as an efficient approach to frailty assessment since CGA is time- and resource-intensive.

Several studies comparing frailty assessment tools have been conducted in the hospital setting. In a multicenter study, four frailty assessment tools that were previously validated in community populations were tested in older adults admitted to medical services in nine hospitals ( $N = 1,306$ ,  $\geq 75$  years, subset of SAFES cohort, France) to

evaluate their predictive ability for cognitive decline, institutionalization, and mortality at one-year follow-up (Dramé et al., 2011). Four multidimensional frailty indexes, *Winograd* (Winograd et al., 1991); *Rockwood* (Rockwood et al., 1999); *Donini* (Donini et al., 2003); and *Schoevaerds* (Schoevaerds et al., 2004) were used to classify patients into three different grades of frailty: G1 indicates not frail; G2 indicates moderately frail; and G3 indicates severely frail. The *Winograd* index included 10 measures that addressed economic and social problems, ADL, balance problems or fall risk, cognitive function, neuropsychiatric status, pressure ulcer risk, nutritional status, comorbidity, polypharmacy, sensory assessment. The *Rockwood* index included 8 measures for ADL and cognitive function. The *Schoevaerds* index included 28 measures that addressed age, living situation, perceived health, ADL, IADL, balance or risk of falls, cognitive function, nutritional status, comorbidity, polypharmacy. The *Donini* index included age, cognitive function, Mini Nutritional Assessment (MNA) which consists of four parts: (a) Anthropometric measurements (questions, BMI, mid-arm circumference, calf circumference, weight loss past three months); (b) Global assessment (living arrangements, number of prescribed medications, psychological stress last three months, mobility, neuropsychological problems, pressure ulcers); (c) Dietary assessment (6 questions, number of meals per day, protein, fruit, vegetable intake, decrease in food intake in last three months, fluid intake per day, ability to eat alone); and (d) Subjective assessment (questions, subjective assessment of patient's nutritional and health status). Laboratory data included serum albumin, lymphocyte count, hemoglobin, WBC, cholesterol, and transferrin.

All patients were classified as frail by at least one of the four indexes. The *Winograd* and *Rockwood* indexes classified patients most often as G2-moderately frail (85% and 96%, respectively), and the *Donini* and *Schoevaerds* indexes classified frailty in patients most often as G3-severely frail (71% and 67%, respectively). Outcome data indicate that 34% experienced rapid cognitive decline, 36% were admitted to an institution, and 34% died. With the *Rockwood* index, all subjects who experienced rapid cognitive decline were classified in as G2-moderately frail; whereas, when the *Donini* and *Schoevaerds* indexes were used rapid cognitive decline was evidenced in those who were classified as G2-moderately frail, and G3-frail. No significant difference was found between frailty grade and rapid cognitive decline, but frailty grade was significantly associated with an increased risk of institutional admission and death for all four frailty indexes. There was poor agreement between the four frailty indexes. This study is the first to compare four frailty indexes in hospitalized medical patients and highlights the limitations of these frailty assessment tools. It is unclear if any of these assessment tools is superior or appropriate for the acutely ill hospitalized adult population.

Given variation in frailty definitions, it is not unexpected that prevalence rates and outcomes differed across studies. Frailty assessment tools may measure different components or domains of frailty. The prevalence of frailty may be over-estimated or underestimated by different tools. Research is needed to determine the psychometric properties of frailty assessment tools to determine frailty constructs and variables, measure validity and reliability, and identify the appropriate populations and settings for

application. Well-designed cross-comparison studies and original research is needed to learn which frailty criteria best characterize or predict frailty in hospitalized adults.

### **Frailty and Hospitalized Adults**

Frailty is commonly viewed as a syndrome that affects the aged, very old, or terminally ill. Much of what is known about frailty is derived from research on those who are at least 65–70 years of age and older based on the premise that frailty is a geriatric syndrome inextricably linked to aging and age-related morbidity. There is little research about frailty in middle-aged adults but there evidence suggests there may be a subgroup at high risk for frailty due to early onset of morbidity, disability, disadvantaged life circumstances, lifestyle (poor nutrition, physical inactivity, obesity), environmental exposures, and other factors. For these reasons, research on frailty in hospitalized adults 55 years of age and older is needed.

The natural history of frailty is indeterminate because there are few longitudinal studies designed specifically for frailty. Research indicates there may be subtypes of frailty or a frailty typology. Frailty is characterized as a dynamic state, a condition of stable instability that is easily disrupted, and that transition between levels of frailty is possible. What are the implications of these findings in acutely ill hospitalized adults? Research indicates that even when the primary medical problem which resulted in hospitalization is resolved, frail person fare worse than nonfrail. The potential positive and negative effects of hospitalization on frailty are not known, but are important in order to separate those factors from the components of frailty that can be directly assessed.

Much of what is known about frailty in community populations may not be transferrable to the hospitalized adult. Some of the strongest predictors of frailty are performance tests of gait, balance, and muscle strength (Ko, 2011). These tests may not be possible to use in acutely ill adults. Research is needed on methodologies to define frailty in acutely ill adults, particularly those who are not able to undergo some of the frailty assessment methodologies because of medical condition or instability.

Frailty is difficult to identify since it is not associated with discrete pathological processes or medical diagnoses that would be expected to be confined to a single organ system with predictable manifestations (Inouye et al., 2007). Distinct causal pathways are indeterminate because defining characteristics are interdependent and overlapping (Kane et al., 2011). Thus, search for a single etiology can be time consuming, costly, burdensome to the patient, and unlikely to yield a definitive diagnosis since multiple factors are involved (Buchner & Wagner, 1992; Inouye et al., 2007; Schwab, 2008). In the hospital setting, identifying frailty is critical to avoid unnecessary, inappropriate, and potentially harmful consequences of diagnostic testing, treatment, and medical, pharmacologic, surgical interventions.

Research indicates that many hospitalized older adults experience functional decline prior to admission. There is a substantial body of literature on the iatrogenic effects of hospitalization on older adults. A cascade of adverse effects can occur in both robust and frail persons. The hazards of immobility, risk for functional decline and other geriatric syndromes related to the stressful hospital environment (disrupted sleep, frequent interruptions by strangers, tests schedule throughout the day, missed meals,

devices and catheters, treatments), poor care coordination, medication errors, injury, and other problems can occur (K. E. Covinsky et al., 2003; Creditor, 1993; Graf, 2006). Some problems are system-related (staffing ratio and mix, resources, policies, procedures, geriatric care practices, management practices), some are staff-related (relationships, patient care quality and safety, person-centered care), and others pertain to informatics (access, acquisition, use of evidence-based knowledge, quality monitoring and care improvement initiatives, benchmarking). Do any of these factors impact incident and prevalent frailty? Do certain medical and nursing care practices create conditions that increase risk for frailty, directly precipitates frailty, or magnifies frailty manifestations in those who are frail persons? Can frailty be propelled along an irreversible course during a hospitalization that was expected to be uneventful? Unplanned 30-day hospital readmission is considered a sentinel event and CMS has begun enforcement of regulations that impose financial penalties on preventable readmissions (CMS, 2012a, 2012b). In a case-control study of older adults in a Medicare managed care plan who experienced urgent 30-day hospital readmission ( $N = 144$ ), five factors significantly and independently associated with readmission were 80 years of age and older ( $OR = 1.8$ ; 95%  $CI$ , 1.02–3.2), prior 30-day readmission ( $OR = 2.3$ ; 95%  $CI$ , 1.2–4.6),  $\geq 5$  comorbidities ( $OR = 2.6$ ; 95%  $CI$ , 1.5–4.7), history of depression ( $OR = 3.2$ ; 95%  $CI$ , 1.4–7.9), and lack of documented patient or family education ( $OR = 2.3$ ; 95%  $CI$ , 1.2–4.5; Marcantonio et al., 1999 ). Research is needed to identify vulnerable subgroups on admission and during hospitalization as health status changes to enact appropriate assessments, prevention, intervention, and discharge planning.

There is a gap in research about the best way to assess frailty in hospitalized adults. Older hospitalized adults have higher comorbidity, greater symptom burden, take more medications, may need more ADL assistance, and experience more geriatric syndromes such as falls, delirium, pain, dehydration, and functional decline (C. C. Chen et al., 2011). Disease focused assessments and care delivery are often ineffective since other problems intertwined with the primary medical problems may not be addressed, or are addressed by other specialists with limited communication and collaboration in care and discharge planning. Most frailty assessment tools have been tested in community, primarily well older adults with stable chronic conditions and many of these tools have been applied in selected groups of acutely ill hospitalized older adults, a population for which they were not designed and it is unclear how to interpret assessment findings. Recent studies have focused on older adults, often 70 years of age and older, admitted for elective surgery in various subspecialties, and oncology and cardiology services. A variety of approaches have been utilized to determine if frailty assessment improves risk assessment and prediction of complications related to surgery, invasive procedures or medical treatment (such as chemotherapy), morbidity, mortality, and length of stay compared to traditional risk assessment tools. Few frailty assessment measures (e.g., gait speed) have been replicated according to original protocols in which the measure was validated as a frailty predictor. Thus the validity and reliability must be considered when interpreting findings. Some frailty measures require complex calculations or norming data according to the study population and may include computations that include gender

and BMI. There are no standardized recommendations for frailty cutpoints for some assessment measures that can be utilized in acutely ill hospitalized adults.

Geriatric medicine has historically utilized comprehensive geriatric assessment (CGA) in hospitalized older adults to comprehensively address multidimensional BPSS needs associated with the primary admission diagnosis(es), engage the patient and family in identifying preferences for care, prevent geriatric syndromes and functional decline, and identify resources for discharge planning. Geriatric medicine is infrequently the primary admitting service for older adults thus access to geriatric expertise and CGA often requires consultation and referral. CGA is administered by an interdisciplinary team to ensure that all relevant BPSS and environmental issues are addressed to ensure optimal quality of care and smooth transition from hospital to home. CGA and effective interdisciplinary team communication and care coordination can reduce length of stay and preventable 30-day readmission.

Most frailty research assesses frailty at one time point. In longitudinal studies, frailty may be assessed at one time point over a period of years. In hospitalized adults, frailty assessment at one time point may characterize frailty at that time point (e.g., on admission) that would be extremely useful in risk stratification and care planning. However, level of frailty is likely to fluctuate during hospitalization and it would be imperative to identify critical data that suggests worsening frailty as well as improvement and recovery. Repeated frailty assessment would be instrumental in provision of timely, person-centered care since rapid adjustments could be made in the care plan as patient

status occurs. These data would be important elements in quality improvement monitoring since the efficacy of interventions and frailty trajectories could be examined.

It is unclear if frailty measures validated in community-living older adults are applicable in acutely ill hospitalized adults. The use of lengthy questionnaires, performance measures such as gait speed, handgrip strength, and chair raises, collection of large amounts of data, and ordering of unconventional biomarkers may not be feasible, safe, applicable, or affordable. However, if a systematic approach to frailty assessment, prevention and treatment is initiated and adopted across health care settings where findings are available in an integrated electronic medical record, crucial information about health status trajectories and responses to acute illness and other stressors would aid in clinical decision-making.

Frailty assessment upon hospital admission, during hospitalization, at discharge, and post-discharge would provide a profile of BPSS function, physiologic stability or dysregulation, and outcomes experienced such as untoward events and complications, new or worse morbidity, mortality, longer length of stay, and hospital readmission.

Recommendations on frailty assessment indicate that performance measures, specifically gait speed, should be included since it is quick and easy to perform, inexpensive, and a strong predictor of frailty (Abellan van Kan et al., 2009; Studenski et al., 2011; Studenski, 2009, 2012). Suitable substitutes are repeated chair stands and balance tests (Cesari et al., 2009). Adoption of performance measures may be challenging, potentially unsafe, even impossible, in some acutely ill hospitalized adults. Issues pertaining to staff training, time, space, equipment, data management, and systems

that codify administration, interpretation, and care-planning require consideration. Timing of administration would influence performance, especially in patients who are medically unstable, have experienced acute trauma, are tethered to multiple monitoring and intravenous devices, and who are on medications that affect gait, balance, and cognition. Gait speed testing has been included in frailty assessment of hospitalized adults admitted to cardiology units or for elective surgery (Afilalo et al., 2012; Purser et al., 2006). A major barrier to frailty assessment in hospitalized adults is limited knowledge among many health professionals about geriatrics, frailty, and care of the elderly with acute and chronic illness from a holistic perspective (AACN, 2011a, 2011b; IOM, 2008).

Before implementation of a frailty assessment protocol on hospital clinical units and across a health system, research is needed to determine frailty components, elements of screening and comprehensive assessment, and validation of frailty assessment models in different hospitalized subgroups (medical, surgical, critical care, specialty practices, etc.). Integration of frail assessment into the EMR using informatics and decision-making algorithms for primary and secondary prevention, targeted intervention, and quality monitoring tracking systems that signal changes in condition based on nursing and interdisciplinary team assessments would optimize timely use of clinical data that could favorably impact quality of care and accelerate recovery. Models of care that include geriatric nurse specialists would facilitate forward movement in this area.

Table 3 lists studies of frailty in hospitalized adults. A wide variety of patient and hospital characteristics, admitting services, and approaches to frailty assessment are

reflected in these studies. Conclusions cannot yet be drawn about best practices for frailty assessment in hospitalized adults. Further research is needed on the validity, reliability, target populations, and utility of frailty assessment instruments and the implications for professional nursing and interdisciplinary team function.

Table 3

## Frailty in Hospitalized Adults

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Fried Frailty Index				
Afilalo et al., 2012  Prospective cohort study  Canada and USA	<i>N</i> = 152, ≥ 70 yrs., 34% women. Elective cardiac surgery patients, CABG or valve procedure, preop assessment.	Fried Frailty criteria and an expanded 7 item scale. Gait speed, 5m walk; handgrip strength, exhaustion, physical activity, weight loss plus cognition (MoCA) and mood (HADS).	Frailty based on Fried Frailty Index: 26%;  Frail based on: -Slow Gait Speed: 46%;	Gait speed best independent predictor for frailty, mortality, major morbidity.  3 or more impairments on
Afilalo et al., 2012 (cont.)	Evaluated/compared 4 frailty measures: 1-CHS scale, 5 item and 7 items 2- MacArthur Study, 4 items 3- Disability scales: Nagi Scale, 7 items, Katz ADL, 6 items, OARS-IADL, 7 items 4-Gait speed, 5m walk	MacArthur Study of Successful Aging-4 items, gait speed, handgrip strength, inactivity, cognitive impairment.  Nagi Disability Scale Katz ADL scale OARS IADL scale	-Nagi Disability Scale: 76%;  -Katz ADL Scale: 32%	Nagi Disability Scale (higher level disability tasks than ADL/IADL) predictive of mortality/ major morbidity.  Measurement of frailty and disability complementary.

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Fried Frailty Index (cont.)				
Gharacholou et al., 2012  Prospective cohort study  USA	<i>N</i> = 545, ≥ 65 yrs. admitted for PCI (percutaneous coronary intervention), pre-procedure assessment.	Fried criteria plus Short-Form-36 and the Seattle Angina Questionnaire.	Frail: 19%; Intermediate frail: 47%; Not frail: 21%	Patients had greater comorbidity, more severe angiographic disease, poorer health status and physical limitations, more angina, lower quality of life than nonfrail.
S. Collins, 2007  Retrospective, correlational study  USA	<i>N</i> = 154, 50-94 yrs, admitted to heart failure center of a large teaching hospital.  Retrospective record review.	Modified Fried Frailty criteria, 3 of 5 of following: BMI <18.5 kg/m <sup>2</sup> or >30.0 kg/m <sup>2</sup> ; Albumin <3.8 g/dl; Hemoglobin <13.5 g/dl for men or <12.5 g/dl for women; NYHA class III or IV heart failure and/or ejection fraction <40%; Iowa Fatigue Scale, score > 35.	Frail: 38%  Anemia: 90% of frail females compared to 28% of frail males (p<.0001)	Females 3X more likely to be frail (p=.002); frail females 27X more likely to be anemic (p<.0001) compared to males. Significant (p =.05) differences in late HF by sex; 80% to 60% of older females. Self-report of poor health
S. Collins, 2007 (cont.)				increased the likelihood of frailty >3X that of self-report of excellent to fair health (p=.002). Those with ≥ 2 chronic illnesses were more than 5X more likely to be frail (p=.042)

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
<b>Deficit Accumulation Index</b>				
R. R. Cohen et al., 2012 Retrospective cohort study USA	<i>N</i> = 102, ≥ 65 yrs., retrospective cohort study, elective abdominal surgery patients, preop assessment.	39 variables in the Deficit Accumulation Index (DAI): morbidity, vision, pain, anemia, albumin, BMI, depression, mobility impairment, arthritis, weight loss, cognitive impairment, pressure ulcer, etc.	Frailty prevalence not specified. Risk of complications increased with greater DAI and Braden Scale scores	Braden Scale score independently predicted post-op complications. The DAI and ASA Class ≥ 3 not predictive of complications.
T. N. Robinson, Wu, et al., 2011 Prospective cohort study USA	<i>N</i> = 233, > 65 yrs., major elective surgery requiring post-operative intensive care unit admission.	14 frailty characteristics for 6 domains: Comorbidity burden (Charlson Comorbidity Index, American Society of Anesthesia score, medications, hematocrit <35%); Function (any functional dependence, Timed Up & Go test); Nutrition (albumin < 3.4 g/dL, BMI, >10 lb. weight loss past 6 months); Cognition (Mini-Cog < 3, depressed mood); Geriatric syndrome (>1 fall past 6 months); Extrinsic frailty (live alone).	Frailty characteristics related to discharge to institution: Charlson Comorbidity Index ≥ 3, hematocrit < 35%, any functional dependence, Mini-Cog score ≤ 3, fall within past 6 months	30% required discharge to institution.  Multivariate logistic regression: Timed Up & Go test ≥ 15 and any functional dependence most closely related to discharge institutionalization.
<b>Multidimensional Frailty Assessment</b>				
Winograd et al., 1991 Prospective cohort study British Columbia	<i>N</i> = 985, study sample = 401, male, ≥ 65 yrs., all patients admitted to medical-surgical units at Veteran's Affairs Hospital.	Independent = independent in all ADLs during acute illness. Frailty = any 1 of 17 criteria (CV, chronic and disabling illness, confusion, dependence in ADLs, depression, falls, impaired mobility, incontinence, malnutrition, polypharmacy, pressure ulcers, prolonged bedrest, restraints, sensory impairment,	Frail: 27%; Independent: 63%; Severely impaired: 10%	Disposition:  Nursing home: Independent- 3% Frail: 34% Severely Impaired: 42% ( <i>p</i> = 0.0001)  Hospital readmission: Independent: 49% Frail: 58% Severely

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Multidimensional Frailty Assessment (cont.)				
Winograd et al., 1991 (cont.)		socioeconomic/ family problems. Severely Impaired = severe dementia and ADL dependence, terminal illness.		Impaired: 51% ( $p = 0.34$ )
D. H. Lee, Buth, Martin, Yip, & Hirsch, 2010  Prospective study  Canada	$N = 3,826$ , all patients admitted for elective cardiac surgery, preoperative assessment.	Katz Index of ADL (5 items, any impairment), Ambulation, Dementia.	Frail: 4.1%	Older, female, more comorbidity (diabetes, COPD, congestive heart failure, RR, cardiovascular disease), higher acuity level, more complex operations.
J. E. Carlson et al., 1998  Prospective cohort study  USA	$N = 122$ , $\geq 60$ yrs., non-elective consecutive admissions to 14-bed acute medical care unit from ED or home.	Modified version of FIM instrument at 4 time points: pre-illness, admission, discharge, 6-months post-discharge. Seven domains rated on 1-7 scale: feeding, hygiene, bathing, toileting, dressing, communication, mobility. Summed score = functional level.	Frail/Poor functional homeostasis, decline of 1 point on FIM: 52%, $n = 64$  No change or increase in FIM: 48%, $n = 58$	Decline in functional status was a significant predictor of adverse outcomes: Readmission, Mortality, Nursing home admission, Functional decline
J. E. Carlson et al., 1998 (cont.)		Frailty defined as substantial amount of functional decline during illness (magnitude and severity); concept of Functional Homeostasis.		
T. N. Robinson, Wallace, et al., 2011  Prospective cohort study  USA	$N = 60$ , $\geq 65$ yrs, elective admission for colorectal surgery.	Abnormalities across 5 domains summed: function (Timed Up and Go test $\geq 15$ seconds, 10 foot walk), dependence in 1 ADL (bathing, dressing, toileting, transferring, continence, feeding), cognition (Mini-Cog)	Nonfrail: 40%; Prefrail: 22%; Frail: 38%	Higher degree of frailty related to increased rates of discharge institutionalization and 30-day readmission.  Frailty status did

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Multidimensional Frailty Assessment (cont.)				
T. N. Robinson, Wallace, et al., 2011 (cont.)		score $\leq 3$ , combination of a 3-item recall and		not differ by cancer tumor stage or site of operation.
T. N. Robinson, Wallace, et al., 2011 (cont.)		clock draw test), albumin $< 3.4$ mg/dL, hematocrit $< 35\%$ , geriatric syndromes ( $\geq 1$ fall past 6 months, Charlson Comorbidity Index $\geq 3$ ., chronic disease burden. Summed score computed for positive indicators. Frailty defined in ordinal scale: nonfrail (0-1 abnormal finding), prefrail (2-3 findings), frail (4-7 findings).		Frailty predicted increased surgical and hospital costs and 6-month health care costs.  Frailty significantly associated with older age, discharge to institution, 30-day readmission.
Freiheit et al., 2010  Prospective cohort study  Canada	$N = 374, \geq 60$ yrs., with coronary artery disease undergoing cardiac catheterization.	Frailty measures for 3 domains: <u>Physical Frailty</u> : balance (tandem balance $\leq 10$ seconds), gait speed (2.4 m walk in $> 4$ seconds) <u>Cognitive Frailty</u> : cognition (Mini-Mental State Exam, lowest decile, Letter-naming fluency test score $\geq 1.5$ SD below the mean, Animal naming fluency test $> 1.5$ SD below mean, Trail Making test, B $\geq 1.5$ SD below mean), poor self-rated health, BMI ( $< 21, > 30$ kg/m <sup>2</sup> ), <u>Psychosocial Frailty</u> : depressive symptoms (Geriatric Depression Scale $> 4$ , Mood-Hope Scale $> 1$ , Withdrawal-Apathy Vigor Scale = 3), Lives alone.	Final Model for frailty was 5 variables:  Poor balance; Abnormal BMI; Depressive symptoms; Cognitive impairment (Trails B); Live alone.  For scores $\geq 3$ , 10 times as likely to have ADL disability, 4 times as likely for poor HRQoL as those with scores of 0.	Brief index was significant predictor of ADL dependence (OARS Multidimensional Functional Assessment Questionnaire) and HRQoL (EuroQOL EQ-5D (mobility, self-care, usual activities, pain or discomfort, anxiety or depression)

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Multidimensional Frailty Assessment (cont.)				
Freiheit et al., 2010 (cont.)		Regression analysis determined 5 best fitting frailty criteria for ADL decline: poor balance, BMI, impaired Trail-Making Test Part B performance, living alone, depressive symptoms. Frailty: $\geq 3$ criteria		
Comprehensive Geriatric Assessment (CGA)				
Rønning et al., 2010  Prospective cohort study  Norway	$N = 187$ , 137 had biomarker data, $\geq 70$ yrs., admitted for colorectal surgery.	Modified CHS Frailty criteria, CGA and serum biomarkers collected within 14 days before surgery.  Frailty determined by mathematical algorithm and based on continuum with “fit” on one end, “frail”  Biomarkers: CRP, IL-6, TNF- $\alpha$ , D-dimer.	Frailty prevalence not reported.  CRP and IL-6 significantly higher in intermediate frail vs fit. CRP above lower quartile significantly associated with ‘any’ ( $OR = 2.18$ ) or ‘severe’ ( $OR = 2.60$ ) complication.	CGA frailty a strong independent predictor for any complications Frailty predicted any and severe post-operative complications. CGA, higher CRP and IL-6 levels.  IL-6 only predictor of severe complications
Hilmer, Perera, et al., 2009  Prospective cohort study  Australia	$N = 111$ , $\geq 70$ yrs., admitted to an Australian teaching hospital, Medical units for aged care, general medicine, cardiology, other  Validated REFS against Geriatrician’s Clinical Impression of Frailty (GCIF) (cognition, function, comorbidity,).	REFS: Reported Edmonton Frailty Scale: Age, General health status, Function (Katz ADL), Cognition (MMSE), Mood, Nutrition, Number of medications, Incontinence, Charlson Comorbidity Index, Social support.  Scoring: range, 0-18: Not frail = 0-5; Apparently vulnerable	Frail = 64%; Nonfrail = 36%  Frail defined by sum score of 8-18, or Moderate to Severe Frailty.	REFS is a Modification of the Edmonton Frail Scale (EFS).  Significant predictors: age, live alone, number of meds.

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Comprehensive Geriatric Assessment (CGA; cont.)				
Hilmer, Perera, et al., 2009 (cont.)		= 6-7; Mild Frailty=8-9; Moderate Frailty=10-11; Severe Frail=12-18.		
Dramé et al., 2008  Prospective cohort study  France	<i>N</i> = 870, validation cohort <i>n</i> = 436, ≥ 85 yrs., 65% female, 2-yr. follow-up.  Patients admitted to geriatric/ medical wards in 9 teaching hospitals. From SAFES cohort (Frail Elderly Subject: Evaluation and Follow-up)	Mortality Risk Index: CGA (Katz ADL, cognition (MMSE), delirium, mood); Physical Performance (One-leg standing balance, Timed Get-Up-and-Go test); Nutrition (Mini-Nutritional Assessment); Comorbidity (Charlson Comorbidity Index); Pressure Ulcer Risk (Norton Scale); Sociodemographics (age, gender, living location, education).  Frailty: Sum of points for each weighted risk factor. Did not define frailty but risk profile approximates other frailty assessments.	3 Frailty Risk Groups: High, ≥ 6: 17%; Medium, 3-5: 56%; Low, 0-2: 17%  Mean score = 4, ( <i>SD</i> , 2); Median, 4; Range, 0-10	Significant mortality predictors: Age, ADL dependence, malnutrition, delirium, high comorbidity, living in institution, female gender (borderline significant).
Kristjansson et al., 2010  Prospective cohort study  Norway	<i>N</i> = 185, ≥ 70 yrs., admitted to hospital for elective colorectal surgery.  CGA conducted within 14 days prior to colorectal surgery.	CGA domains: <u>Function</u> (Nottingham Extended Activities of Daily Living, Barthel Index), <u>Comorbidity</u> (Cumulative Illness Rating Index (CIRS)), <u>Cognition</u> (MMSE), <u>Mood</u> (GDS), <u>Nutrition</u> (Mini Nutritional Assessment [MNA]), <u>Polypharmacy</u> (number used daily, ≥ 5).	Fit: 12%; Intermediate: 46%; Frail: 43%	CGA can identify frail patients with significantly increased risk of severe post-operative complications. 62% of frail patients experienced complications, compared to 33% of fit, 36% of intermediate frail.

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Comprehensive Geriatric Assessment (CGA; cont.)				
Kristjansson et al., 2010 (cont.)		Frailty: >1 of PADL <19, CIRS, any grade 4 comorbidity, <2 comorbidities grade 3, MMSE < 24, GDS, >13, MNA < 17, > 7 daily meds.		
Kristjansson et al., 2010  Prospective cohort study  Norway	<i>N</i> = 178, ≥ 70 yrs., elective surgery for suspected or confirmed colorectal cancer, recruitment from 3 hospitals, one a referral hospital for elective surgery.	CGA domains: <u>Function</u> (Nottingham Extended Activities of Daily Living [NEADL, 22 items, independence in mobility, kitchen, domestic, leisure activities; 4-point scale, range 0-66.] and ADL Barthel Index, 6 items), <u>Comorbidity</u> (Cumulative Illness Rating Index [CIRS]), <u>Cognition</u> (MMSE <24), <u>Mood</u> (GDS ≥ 14), <u>Polypharmacy</u> (meds used daily, ≥ 5), <u>Nutrition</u> (Mini Nutritional Assessment [MNA], 18 items), appetite, weight loss, diet, self-perceived health, mid-arm and calf circumference.  MNA Score- summed scores for items, range 0-30: Score 17.5-23.5 = Risk for malnutrition; Score <17 = Malnutrition.	Fit: 12%; Intermediate frail: 46%; Frail: 43%  Severe complications occurred in 33% of fit, 36% of intermediate frail, 62% of frail.	83% had severe complications, 3 deaths. 61% had ≥ 1 severe complication.  Age, American Society for Anesthesia (ASA) class, or tumor stage not associated with complications.  Frail vs nonfrail increased <i>RR</i> of for any complication and severe complication, 1.59 and 1.75, respectively.  CGA identified frail patients who have significantly greater risk of severe complications. Most common: wound infection, UTI, pneumonia or ventilator assistance, cardiac (angina, MI, arrhythmia, lung edema), delirium, intra-abdominal

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Comprehensive Geriatric Assessment (CGA; cont.)				
Kristjansson et al., 2010 (cont.)		<p>Frail = &gt;1 of ADL &lt;19, CIRS, any grade 4 comorbidity, &gt;2 comorbidity grade 3, &gt;7 daily meds, MNA &lt; 17, MMSE &lt; 24, GDS, &gt;13</p> <p>Frail, higher risk for severe complications in colon cancer patients: <i>OR</i> = 3.70; 95% <i>CI</i>, 1.74-7.88.</p>		abscess.
<p>Makary et al., 2010</p> <p>Prospective cohort study</p> <p>USA</p>	<p><i>N</i> = 594, ≥ 65 yrs., 84% Caucasian, 42% female, admitted to academic medical center for elective surgery, nonrandom selection. Exclusion: Parkinson's disease, CVA, MMSE &lt;18, taking carbidopa/levodopa, donepezil hydrochloride, anti-depressants.</p>	<p>CHS frailty criteria; frail = 4-5 criteria, intermediate frail = 2-3 criteria, nonfrail, 0-1 criteria.</p> <p>Scoring validated in study by grouping of ORs for outcomes in exploratory data analysis.</p>	<p>Frail: 10.4%; Intermediate frail: 31%; Nonfrail: 58.3%</p> <p>Comorbidity-Frail/ Nonfrail: Hypertension: 70.5% /57.8%; Arthritis: 29.5% /15.9%; Diabetes: 21.3%/ 17.4%; Heart failure: 14.8% / 3.8%; COPD: 14.8%/ 6.4%; Cancer: 54.1% /74.1%.</p>	<p>Frailty an independent predictor of surgical complications in adjusted models.</p> <p>Intermediate frail patients had 2.06 higher OR, 95% CI, 1.18-3.60) of complications, Frail had 2.54 times higher OR, 95% CI, 1.12-5.77.</p> <p>Mean LOS significantly higher in frail; independently predicted LOS in all adjusted</p>

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Comprehensive Geriatric Assessment (CGA; cont.)				
Makary et al., 2010 (cont.)				<p>analyses.</p> <p>Mean LOS for Minor procedure, Frail vs Non-frail: 1.5 vs 0.7 days; For Major procedure, Frail 4.2 vs 6.2 days in Nonfrail.</p> <p>Frailty independent predictor of discharge to assisted living or nursing home.</p> <p>Frailty assessment enhanced predictive power of ASA, Lee, and Eagle scores.</p>
T. N. Robinson et al., 2009  Prospective cohort study  USA	<p><i>N</i> = 110, ≥ 65 yrs., admitted for major surgery requiring postoperative intensive care unit admission, 95% male, surgeries mostly abdominal/general, urology, thoracic, vascular.</p>	<p>5 Frailty domains: Age, cognition (Mini-Cog Test), chronic under-nutrition (weight loss past 6 months, BMI, albumin), falls past 6 months, depression (clinical history), anemia (hematocrit within 30 days of surgery).</p> <p>Disability (Katz ADL) and Comorbidity (Charlson Comorbidity Index) also assessed for comparison.</p>	<p>Incident mortality at 6 months: 15%</p> <p>Post-discharge institutionalization: 26%</p> <p>Frailty predictors significant for mortality and discharge institutionalization: cognition, BMI, albumin, falls, Katz ADL, hematocrit; and Charlson Comorbidity Index.</p>	<p>Frailty assessment superior or adjuvant to preoperative assessment that is focused on single organs or end-organ functional deficits and risk stratification based on outcomes for single organ system (e.g., cardiac). Outcomes relevant to elderly: functional status, recovery, institutionalization mortality.</p>

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Comprehensive Geriatric Assessment (CGA; cont.)				
<p>Pilotto et al., 2012</p> <p>Prospective multicenter cohort study</p> <p>Italy</p>	<p><math>N = 2,033, \geq 65</math> yrs., admitted to 20 geriatric units in hospitals across regions of Italy.</p> <p>Frailty Assessment included 4 frailty indexes that reflect 3 conceptually different frailty approaches:</p> <p><u>Phenotype:</u> Frailty Index-Study of Osteoporotic Fractures (FI-SOF);</p> <p><u>Deficit Accumulation:</u> Frailty Index-Cumulative Deficits (FI-CD);</p> <p><u>Multi-dimensional Multidimensional:</u> Prognostic Index (MPI), Function Index, Comprehensive Geriatric Assessment (FI-CGA).</p>	<p><u>FI-CGA:</u> 10 domains, cognition, mood and motivation, communication, mobility, balance, bowel function, bladder function, ADL, IADL, nutrition, social resources.</p> <p><u>FI-SOF:</u> 3 items- low energy, unintentional weight loss, 5 chair stands, level.</p> <p><u>FI-CD:</u> 32 items, ADLs, IADLs, Parkinson's disease, arthritis, stomach problems, MI, hypertension, stroke, hip fracture, broken bones, bowel/ bladder problems, dementia, self-rated health, vision/ hearing deficits, problems with teeth, feet.</p> <p><u>MPI-</u> 8 domains: ADL, IADL, cognition (Short Portable Mental Status Questionnaire, comorbidity (Cumulative Illness Rating Scale), nutrition (Mini-Nutritional Assessment), pressure ulcer risk (Exton-Smith Scale), number of meds, living arrangement.</p>	<p>All frailty indexes were significantly associated with 1-month and 1-year all-cause mortality in crude and age- and sex-adjusted models.</p> <p>The MPI had significantly greater discriminatory accuracy than other three at 1 month and 1 year based on area under the ROC curve.</p>	<p>Findings suggest multidimensional MPI was better at predicting mortality than other indexes, e.g., FI-CGA (based on count of impairments) compared MPI (included standardized scales, can be graded and also used as continuous scale to assess change over time).</p> <p>MPI predicts mortality in patients without functional limitations, with malnutrition, comorbidity, and high number of drugs.</p> <p>The FI-SOF had the poorest accuracy.</p>

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Comprehensive Geriatric Assessment (CGA; cont.)				
Sündermann, Dademasch, Praetorius, et al., 2011  Prospective multicenter cohort study  Germany Switzerland Sündermann, Dademasch, Praetorius, et al., 2011 (cont.)	<i>N</i> = 400, ≥ 74 yrs., 52% female, admitted for cardiac surgery (22.5% revascularization, 32% valve, 30.5% combined procedures).  Comprehensive Frailty Assessment compared to 2 other risk assessments: EuroSCORE and Society of Thoracic Surgery (STS) Score.	Comprehensive Frailty Assessment: Modified Fried Frailty Index-grip strength, self-reported exhaustion, gait speed, physical activity assessed via IADL scale, omitted weight loss; plus physical performance measures: balance tests, chair stands, pick up pen from floor. Labs: albumin, creatinine, BNP. Pulmonary function: FEV1 (forced expiratory volume in 1 second).  Scoring: Nonfrail = 1-10 points Intermediate frail = 11-25 points Frail = 26-35 points.	Frail: 21.7%; Intermediate Frail: 7.8%; Nonfrail: 3.6%  Median frailty score = 11 or Intermediate frail.	Overall 30-day mortality, 5.5%. Frailty significantly related to 30-day mortality.  Significantly higher frailty score associated with valve surgery.  Frailty score compared to EuroSCORE and STS Score: low/moderate correlation. ROC curves plotted, AUC scores: EuroSCORE: 0.79 STS Score: 0.76 Frailty Score: 0.71
Fukuse, Satoda, Hijiya, & Fujinaga, 2005  Prospective cohort study  Japan	<i>N</i> =120, ≥ 60 yrs., admitted for thoracic surgery.  CGA done within 2 weeks of surgery.	Frailty characterized using CGA domains: function (Barthel Index), nutrition (BMI, arm circumference, albumin, transferrin, lymphocyte count, cholinesterase level), cognition (MMSE), negative emotions for operation.	ADL dependence and impaired cognition significant predictors of postoperative complications, especially when operation time is long.	Multiple logistic regression found MMSE (56% vs 14%) and Barthel Index (44.4% vs 14%) best model for predicting complications.  Smoking and comorbidity also related to complications.

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Single Measure of Frailty				
Afilalo et al., 2010  Prospective cohort study  Canada, USA	<i>N</i> = 131, ≥ 70 yrs. Elective cardiac surgery (CABG, valve) Four tertiary care hospitals.	Gait speed: 5m walk at comfortable pace. Slow gait speed an indicator of frailty.  Frail/"slow walkers"- gait speed ≥ 6s over 5meters.	Frail/Slow walkers: 46%	Gait speed an independent predictor of outcomes –major morbidity, mortality ( <i>OR</i> = 3.05; 95% <i>CI</i> , 1.23-7.54.  More likely to be female, diabetic.  Outcome: 23% - inhospital mortality or major morbidity.
Jarret et al., 1995  Prospective cohort study  USA	<i>N</i> = 193, ≥ 65 yrs., admitted to large tertiary care university hospital, general medicine service to examine atypical presentation of illness and frailty in hospitalized older adults.	Classified as frail based on Barthel Index score: Frail score < 95 ( <i>n</i> = 117) Well score ≥ 95 ( <i>n</i> = 76)  Feeding, bathing, dressing, grooming, bladder, bowels, toilet use, transfers bed to chair, mobility on level surface-ambulation, stairs. Score range, 0- 100, where higher scores indicate worse function.  Outcomes: death, nursing home admission, long LOS, fail to regain premorbid functional status.	Frail: 41%; Nonfrail: 18%	Frail elders significantly more likely to present atypically on admission, be older, female, less likely to be from community.  Frail significantly more likely to have delirium (61% vs 25% in nonfrail), had more adverse hospital outcomes (e.g., functional decline, restraints, nighttime sedation, pressure ulcers, long LOS) than nonfrail. Premorbid functional dependence ( <i>OR</i> = 2.48), functional decline at admission ( <i>OR</i> = 5.64), atypical presentation ( <i>OR</i> = 2.37), each

Table 3. (Cont.)

Study	Sample	Frailty Criteria and Definition	Frailty Prevalence	Findings
Single Measure of Frailty (cont.)				
Jarret et al., 1995 (cont.)				independently predicted poor outcomes, but disease severity, age, sex did not.
Oster et al., 2004  Prospective study  USA	$N = 322, \geq 65$ yrs., admitted to a geriatric hospital.	Gait speed $>1.0$ meter/second an indicator of independence, $< 0.6$ m/s abnormally slow, associated with functional decline	Mean gait speed 0.53 m/s, abnormal, associated with functional decline	Slower gait speed associated with longer length of stay.  Slower gait speeds, $< 0.40$ m/s had significantly decreased odds of discharge home.
Comparison of Frailty Assessment Tools used in Hospitalized Adults				
Purser et al., 2006  Prospective cohort study  USA	$N = 309$ consecutive admissions, $\geq 70$ yrs.  Cardiology patients admitted for elective cardiac catheterization.	Composite A (Fried Frailty Index); Composite B (Deficit Accumulation); Gait speed ( $\leq 0.65$ m/s); Handgrip strength ( $\leq 25$ kg); Chair stands.  Both Composite A and B groups had higher prevalence of heart failure, cerebrovascular disease, prior CABG, depression than overall cohort.	Frailty: Composite A: 27%; Composite B: 63%;  Gait speed: 50%; Handgrip strength: 50%; Chair stands: 56%.	Gait speed best independent predictor of frailty and other poor outcomes.  ROC analysis done for gait speed, handgrip strength, chair stands to determine cutpoints.  Frailty by any measure significantly associated with mortality.

### Health Care Delivery in Hospitals

In hospitals, clinical care is distinguished by specialty-focused practice where one medical or surgical service assumes responsibility for the patient on admission based on

the primary diagnosis. This is appropriate and efficient in focusing expertise on the main problem to diagnose, treat, cure or stabilize, and discharge. Patients with multiple medical problems, who are medically complex or have a high illness acuity level, or who experience adverse events or syndromes are not easily managed by a single medical specialty. Medical problems in adults are rarely due to a single entity and initial signs and symptoms arise from multiple interacting medical problems, medications, and syndromes that do not match textbook presentation or can be resolved based on linear cause and effect assumptions (Inouye et al., 2007; Jarrett et al., 1995). Atypical presentation is the most common manifestation of illness in the elderly (Berman, Hogan, & Fox, 1987; Jarrett et al., 1995). In a study of hospitalized older adults, less than half of presented on admission with symptoms of disease consistent with the classic medical model that permits appropriate diagnosis and treatment (Fried, Tangen, et al., 2001). Jarrett et al. (1995) examined atypical illness presentation in hospitalized older adults classified as frail or nonfrail based on the Barthel Index of ADL function ( $N = 193, \geq 65$  years). More frail elders presented atypically (41% versus 18% nonfrail), were significantly more likely to present with delirium (61% versus 25%) and had more adverse events (e.g., functional decline, restraints, nighttime sedation, pressure ulcers, longer length of stay) than nonfrail elders.

Thus, frailty does not fit into the traditional biomedical model for defining disease and treatment. A precept in medicine is “not to multiply causes unnecessarily” which means that modern medicine is based on the importance of identifying a single etiologic disease mechanism that can be treated (Schwab, 2008, p. 363). Short and long term goals

may be at odds with one another (e.g., rapid stabilization and/or cure of medical condition and discharge versus chronic disease management and health-promoting self-care and lifestyle behaviors). The biomedical approach does not adequately address the needs of an aging population with multiple medical problems that are intrinsically related to one another and to other biopsychosocial factors.

Interdisciplinary team collaboration is a hallmark in geriatrics. More direct involvement of interdisciplinary teams facilitates care coordination and discharge planning but there is risk that care may be fragmented and communication limited (N. A. Brown & Zenilman, 2010; Molina-Garrido & Guillen-Ponce, 2010; Puts et al., 2010; T. N. Robinson et al., 2009). The complexity and ambiguity of frailty requires diversity in the health care team in order to address BPSS issues and concerns for inpatient care and discharge planning. Geriatric consultation services and interdisciplinary teams can be mobilized by nursing leadership at the bedside in frailty assessment, risk stratification, and care coordination with geriatrics, interdisciplinary teams, and discharge planners.

### **Hospital Length of Stay and 30-Day Readmission**

Frailty is associated with longer length of stay and high rates of hospital readmission. Data from the U.S. National Hospital Discharge Survey for 2007 report that although persons 65 years of age and over account for 13% of the population, they account for 37% of hospital discharges, and 43% of hospital days (Hall et al., 2010). The average length of stay for those 65 years of age and older was 5.6 days compared to 5.1 days for those 45 to 64 years of age (Hall et al., 2010). Increased length of stay may be due to greater medical complexity and acuity, new morbidity, surgery or treatment-

related complications, injurious or untoward events (e.g., falls, injury, delirium, pain, functional decline), poor response to rehabilitation and other treatment, inadequate social support, and complex discharge planning. Unplanned hospital readmission within 30-days of discharge is considered a sentinel event that may be due to poor inpatient quality of care, disease instability at discharge, relapsed medical condition, development of a new problem, medication problems, significant functional decline and dependence with inadequate social support or access to health and social services, and need for terminal care (Marcantonio et al., 1999; Williams & Fitton, 1988).

Length of stay and hospital readmission may be an indication of poor health status and health disparities. Limited achievement of Healthy People 2010 goals point to the need for new approaches to identify and address factors that impede achievement of better health outcomes in vulnerable populations (Healthy People 2020, 2013). Relationships between social determinants, health disparities, and frailty are relevant in acutely ill hospitalized adults and require further study especially with respect to transitions in care (Karunanathan et al., 2009; Morley et al., 2006; Szanton, Seplaki, et al., 2010; Szanton, Thorpe, et al., 2010; Whitson et al., 2011).

There is sufficient evidence that frailty is a formidable public health problem with important implications for hospitalized adults and the health care system. Assessment of frailty using a BPSS-Stress model provides a comprehensive portrayal of the person and the inter-relatedness of health and illness status and function, medical problems and symptoms, sociodemographic characteristics, lifestyle behaviors, and psychosocial-spiritual factors in the context of multidimensional, multifactorial frailty. Frailty

assessment offers a proactive approach that fosters interdisciplinary communication and collaboration in the early identification of frailty indicators to guide strategic prevention and intervention to improve care and health status outcomes.

### **Summary of the Science of Frailty**

Frailty is a physiologically complex, multidimensional syndrome where systemic regulatory functions that normally stabilize homeostasis are compromised. Functional homeostasis is the ability to accommodate change and stressors associated with aging and disease processes without marked physiologic decompensation or functional decline. Research suggests that frailty is due to failure of physiologic defenses and loss of system redundancies that progressively leads to cellular and organ dysfunction across multiple systems (Fried et al., 2009; Krabbe et al., 2004; Nowak & Hubbard, 2009). Normal biologic aging is highly variable and produces only modest reduction in the capacity of cellular and organ systems to effectively and respond to the changing internal milieu of bodily functions (Bortz, 1982, 1993; Fried et al., 2004; Weiss, 2011). These changes are often inconsequential and do not adequately explain how aging independently or synergistically influences frailty (Bortz, 1993). Age, disease, and disability are often used interchangeably as indicators of frailty but their relationships are unclear and manifestations of each can overlap (Ferrucci et al., 2004; Fried et al., 2004; Grealey, 1997; Hadley et al., 1993; P. O. Lang et al., 2009). Evidence of frailty without functional decline, disease, or disability, or advanced age challenges traditional understanding of aging and disease processes since about one-quarter of frail older adults have neither

comorbidity nor disability (Fried, Tangen, et al., 2001; Fried et al., 2004; Inouye et al., 2007; Paixao & Pruber de Queiroz Campos Araujo, 2010; Walston et al., 2006).

Frailty is due to vulnerability arising from the interplay of aging, pathophysiological, genetics, epigenetics, psychological, social, economic, and environmental factors, and other determinants, including early life circumstances and chronic stressors that have long term physiologic consequences (Ahmed et al., 2007; J. E. Carlson et al., 1998; Gouin, Hantsoo, & Kiecolt-Glaser, 2008; Kuh, 2007; Newman et al., 2001; Rockwood et al., 2005). Frailty is characterized by poor physiologic response to minor intrinsic or extrinsic stressors that would not typically produce decompensation and adverse sequela in nonfrail persons (Levers et al., 2006; Whitson et al., 2007). Physiologic dysfunction may be clinically silent until a stressor of sufficient magnitude exceeds the threshold for effective, adaptive responses (Kuh, 2007; Mitnitski, Graham, et al., 2002; Xue, 2011). Failure of compensatory mechanisms precipitate a cascade of adverse events with potentially catastrophic short and long term outcomes (De Lepeleire et al., 2009; Whitson et al., 2007; Xue, 2011).

Common features of frailty do not fit a classic disease model (Jarrett et al., 1995). There are no validated diagnostic markers, signs or symptoms, or laboratory tests that diagnose frailty. The traditional cause-and-effect medical model fails to accurately portray frailty since established diagnostic criteria are lacking (Fried, Storer, King, & Lodder, 1991; Fried, Tangen, et al., 2001; Inouye et al., 2007; Jarrett et al., 1995). Environmental factors and social determinants of health require further investigation in frailty (Kuh, 2007; Szanton et al., 2005). Extrinsic factors such as inadequate access to

health care, poor quality of care, unhealthy living environments, low income, limited education, lack of health and social services, transportation, and appropriate types of social support increase biopsychosocial risk for illness, disease, disability, and frailty (Abellan van Kan et al., 2010; Heath & Phair, 2009; T. Seeman et al., 2007; Szanton, Seplaki, et al., 2010; Szanton, Thorpe, et al., 2010).

### **Gaps in the Literature**

There are significant gaps in the literature about frailty in middle-aged and older hospitalized adults. First, there is a lack of knowledge about frailty in professional nursing as evidenced by limited nursing research and substantive publications, inattention to frailty assessment, prevention, and treatment in clinical practice, and the absence of clinical practice or research conceptual models for frailty to facilitate innovation in clinical practice and research (Burnside, 1990; Campbell, 2009; Fugate Woods et al., 2005; Lekan, 2009; Szanton et al., 2009; Szanton, Seplaki, et al., 2010). Much of the nursing literature on frailty has focused on supportive care of the very old and prevention of functional decline (Boltz et al., 2008a; Campbell, 2009; Dayhoff, Suhreinrich, Wigglesworth, Topp, & Moore, 1998). A significant gap is the absence of a nursing diagnosis for frailty in The North American Nursing Diagnosis Association (NANDA) International 2012–2014 edition (NANDA International, 2011). This omission underscores the need for nursing to examine this syndrome from the nursing perspective and bring it into mainstream nursing through codification as NANDA-endorsed nursing diagnosis (Hilmer, Perera, et al., 2002).

Many health providers including the nursing workforce are under-prepared to address the complex needs of frail hospitalized adults and improve clinical outcomes (IOM, 2008). Prelicensure and continuing nursing education programs are lacking in content that addresses geriatrics, gerontological nursing, and frailty for classroom instruction and clinical application in practice. National initiatives to enhance geriatric nursing education and clinical practice have been strongly advocated by professional nursing groups and nursing education credentialing organizations such as the American Association for Colleges for Nursing and the National League for Nursing . This study provides descriptive data about frailty in hospitalized adults 55 years of age and older, a much younger age group than is customarily studied in frailty research, and preliminary evidence for a practical, clinically relevant approach for assessing level of frailty that would guide development of education and clinical practice initiatives.

Second, the holistic, multidimensional, BPSS-Stress conceptual model is needed in frailty research and clinical practice to provide coherence in structuring systems of care that integrates nursing, medicine, and the interdisciplinary team in action-oriented communication, collaboration, and care coordination (Gilliss, 2011; V. Lee, Fletcher, Westley, & Fankhauser, 2004; Lekan, Hendrix, McConnell, & White, 2010; Levers et al., 2006). Interdisciplinarity is a hallmark of geriatric care but may not be collaborative in clinical nursing practice. Rather, interdisciplinary practice in hospital settings may operate in isolation and only when acute complex care issues arise do team members together engage in purposeful collaboration with the patient and family. In hospital settings, greater reliance on consultation notes and few opportunities for substantive

discussion is more common. This often leads to communication, incomplete, conflicting, or inaccurate information about patient and family goals, preferences and needs and fragmented care and discharge planning. Systematic processes to facilitate interdisciplinarity could have considerable impact on quality of care and outcomes, morbidity, cascade iatrogenesis, length of stay, and hospital readmission (Gilliss, 2011; Potts et al., 1993). The BPSS-Stress model provides a natural platform for team collaboration. Research is needed on how informatics and decision algorithms can be integrated into the electronic medical record to more readily and easily facilitate adoption of frailty assessment in concert with interdisciplinary team communication and care coordination to accelerate implementation of best practices in the care of frail hospitalized adults.

Third, the inclusion of four common biomarkers associated with inflammation and stress is a novel component of frailty assessment in hospitalized adults. Plasma biomarkers provide objective evidence of biologic function that is pertinent to frailty, stress, and disease burden. The significance of the biomarkers used in this study in frailty assessment in acutely ill hospitalized adults is unclear. Research supports a significant inflammatory component in the frailty syndrome, and recent consensus conferences endorse the inclusion of biomarkers in frailty assessment. However, there is a gap in understanding of the role of biomarkers in frailty assessment in hospitalized adults, including which biomarkers should be used, when should they be procured and how often, what reference ranges are appropriate for frailty assessment, and how should the values be interpreted (Blaum et al., 2009; Clark et al., 2007; Gruenewald et al., 2006;

Gruenewald et al., 2009; Kuchel, 2009; Ranjit, Diez-Roux, Shea, Cushman, Ni, & Seeman, 2007; Schmaltz et al., 2005; Szanton et al., 2009; Topinková, 2008). There was no other published account identified in the literature that examined these four biomarkers in a hospitalized adult population 55 years of age and older.

Fourth, the impact of demographic trends have received little attention with respect to frailty, including: (a) the rapidly growing older adult population and increased longevity; (b) earlier onset and prevalence of chronic disease and disability that is intensified by increasing incident obesity at all ages; (c) anticipated increased health care utilization; (d) the need for a wider variety of community-based health and social services and other supportive resources with the capacity to meet increasingly diverse population needs; (e) the growing sociocultural diversity that has implications for health care, health literacy, health promotion, prevention and treatment of frailty; and (f) changes in family structure and caregiving that place greater emphasis on local informal and formal organizations for community-based services (Raphael et al., 1995). The expected increase in the incidence and prevalence of frailty as a result of these trends has significant public health implications. There is strong evidence that health promotion and disease prevention early in life could prevent or reduce incident frailty. Thus innovative, cultural- and age-relevant, multi-factorial public health initiatives are imperative to promote health and well-being, active life expectancy, and compression of morbidity (Bortz, 1993; Fries, 1980, 1988; Raphael et al., 1995; Walston et al., 2006).

Fifth, there is substantial research on functional decline during hospitalization (K. E. Covinsky et al., 2011; Creditor, 1993; de Saint-Hubert et al., 2010; Gill et al., 2008,

2009, 2010, 2011; Mitty, 2010). Functional decline has been proposed as a proxy for frailty because functional decline is an outcome of frailty in the literature (de Saint-Hubert et al., 2010). Functional decline and frailty are in many ways distinctly different. However, with increasing age, there can be substantial overlap even in nonfrail older persons. There is insufficient evidence on differentiating risk for functional decline from risk for frailty to identify those most likely to benefit from prevention, prehabilitation, rehabilitation, and individualized, culturally appropriate intervention.

Finally, there is an important gap in knowledge what differentiates frailty from failure-to-thrive (FTT). These terms are used interchangeably but FTT and frailty are not synonymous (Berkman, Foster, & Champion, 1989; Lunney, Lynn, Foley, Lipson, & Guralnik, 2003; Verdery, 1997a, 1997b, 1998; Woolley, 2004). FTT is a term derived from the pediatric literature that describes infants who are developmentally delayed and fail to gain weight (Berkman et al., 1989; Newbern & Krowchuk, 1994; Braun, Wykle, & Cowling, 1988; Sarkisian & Lachs, 1996). In geriatrics, FTT, or GFTT, describes older adults who mirror the pediatric profile and present with various medical and psychological problems, vague symptoms, impaired ADL and IADL function, malnutrition, weight loss, cognitive impairment, fatigue, depression, and social withdrawal (Newbern & Krowchuk, 1994; Braun, Wykle, & Cowling, 1988; Sarkisian & Lachs, 1996; Woolley, 2004). GFTT may also present as non-response to interventions, appearance of helplessness and hopelessness, and acceptance of death by giving up (Braun et al., 1988; Newbern & Krowchuk, 1994; Berkman et al., 1989; Roth, 2001). The IOM defines FTT in late life as weight loss > 5%, poor nutrition, and inactivity that may

be accompanied by depressive symptoms, dehydration, low cholesterol level, and impaired immune function (IOM, 1991). Robertson and Montagnini (2004) define GFTT as impaired physical and cognitive function, malnutrition, and depression. Clinical features of GFTT appear to mirror some features of frailty.

Despite increased scientific research on frailty, there is no substantive research on GFTT nor are there validated assessment tools for either. Despite this, there is an ICD-9 (International Classification of Disease-version 9) code for FTT in adults, but not frailty. Frailty may be inaccurately coded as FTT. GFTT has not garnered as much attention by researchers as has frailty but it is important that defining characteristics that differentiate GFTT from frailty be determined. Since the natural history of frailty is unclear and may display multiple typologies (Xue, 2011), it is unclear if GFTT represents the end-of-life phase of frailty or is a distinct phenomenon. Current perspectives of GFTT suggest that it represents a terminal, irreversible, end-of-life state with no hope for remediation (Raudonis & Daniel, 2010). The term FTT or GFTT may reinforce negative ageist stereotypes and impede the urgent search for treatable, reversible causes of clinical deterioration (Braun, Wykle, & Cowling, 1988; Sarkisian & Lachs, 1996; Woolley, 2004). Without an evidence base for GFTT, health provider attitudes of resignation, passivity, and therapeutic nihilism may be a powerful driver in clinical decision-making that may deny or fail to justify appropriate treatment (Berkman et al., 1989; Robertson & Montagnini, 2004; Whooley, 2004). Abandonment of the term FTT and GFTT has been recommended (Whooley, 2004). Research is needed to close the gap in understanding the relationship between FTT and GFTT and frailty.

## Chapter Summary

Frailty is a syndrome that predisposes at-risk or vulnerable adults to a myriad of adverse outcomes resulting from the accumulation of decrements in physiologic processes and dysregulation in regulatory mechanisms across multiple organ systems that arise from interactions of age-associated changes, overt and subclinical disease, and BPSS and environmental factors (Fried et al., 2004; Newman et al., 2001). The net effect is a profound decrease in compensatory reserve and the ability to effectively respond to stressors. Acute and chronic, cumulative stress and low-grade chronic inflammation contribute to the pathogenesis of frailty and differentially increases risk for accelerated aging, morbidity, disability, mortality, and other adverse outcomes. Research is needed to better understand frailty indicators, signs, and symptoms and their co-occurrence and trajectories so that appropriate assessment and interventions can be implemented when they are most likely to be effective (Cesari, 2011; Newman et al., 2001; Whitson et al., 2007). This is especially important in hospitalized adults where prolonged periods of immobility and a cascade of adverse events, or “cascade iatrogenesis” (Potts et al., 1993, p. 199) may develop with deleterious consequences despite stabilization or resolution of the primary medical or surgical problems (Creditor, 1993; Lafont et al., 2011; Lefevre et al., 1992; Mitty, 2010; Olson et al., 1990). Identification of persons at risk for frailty or who are frail would facilitate the nursing process and clinical decision-making regarding targeted prevention, intervention, and discharge planning.

Frailty assessment in hospitalized adults is important because clinical instability signals a critical time of high risk for a multitude of adverse health events and outcomes

(Lafont et al., 2011; Lefevre et al., 1992; Mitty, 2010; Potts et al., 1993). This preliminary descriptive study of frailty utilizes existing clinical data and biomarkers readily available to nurses and is an important first step in understanding frailty in this under-studied population.

Frailty is an important public health issue since it is a predictor of morbidity, disability, longer length of stay, hospital readmission, need for continued care, institutionalization, increased health care utilization and costs, and shortened life span (Rantz, Marek, & Zwuygart-Stauffacher, 2000; Woo et al., 2006). Demographic data projecting continued growth and increased longevity in the aging population highlights the importance of frailty since its incidence is expected to increase. Frailty exacts a high cost in terms of dependency, excess disability, personal suffering, caregiver burden, and quality of life (Abellan van Kan et al., 2010; Fillit & Butler, 2009; Grenier, 2002; Mezey & Fulmer, 1998).

## **CHAPTER III**

### **METHODS**

This retrospective, cross-sectional, descriptive study examined frailty in adults 55 years of age and older who were admitted to the general medicine, cardiology, or orthopedic services at a large academic medical center in central North Carolina during a 15-month time frame. A descriptive study design was selected since there is limited empirical research on frailty in hospitalized adults. A conceptual model was used to guide description of frailty since this construct is ambiguous and poorly understood. This study explored the statistical and clinical significance of relationships between biologic, psychological, social, spiritual, and demographic variables and frailty in hospitalized adults. Access to existing clinical data from the electronic medical record (EMR) facilitated working with a larger sample and wider range of variables than may be feasible in a prospective study.

The purpose of the study was to characterize frailty in hospitalized adults and to determine if level of frailty, represented as a Frailty Score, predicted hospital length of stay and 30-day hospital readmission.

#### **Sample**

The study sample was a purposive, convenience sample of hospitalized adults. Inclusion criteria were (a) 55 years of age and older on the date of hospital admission; (b) admission to one large academic medical center in central North Carolina; (c)

admission to general medicine, cardiology, or orthopedic service; (d) date of admission occurred during a 15-month time frame, June 1, 2010 through August 31, 2011; (e) hospital admission included an overnight stay; and (f) hospital encounter had complete data for age, gender, race/ethnicity, date of admission, date of discharge, and laboratory data for plasma C-reactive protein (CRP) or hs-C-reactive protein (hs-CRP), albumin level, hemoglobin concentration, and white blood cell (WBC) count. For patients meeting study inclusion criteria with more than one hospital encounter during the study time frame, the first encounter with complete data as specified above was selected. Exclusion criteria were diagnosis of cancer, excluding dermatologic cancers, and undergoing active treatment and hospital length of stay less than 24 hours without an overnight stay.

## **Setting**

### **State Characteristics**

North Carolina (NC) is located in the Southeastern U.S. and is diverse across many sectors, especially population characteristics, geography, and employment. In 2010, North Carolina ranked 10<sup>th</sup> in the U.S. in population. The population estimate in 2011 was 9,656,401, which represents an 18% increase from 2000 to 2010 (U.S. Census Bureau, 2012). Much of the population growth has occurred in the cities of Charlotte (731,424; 35.2% increase), Raleigh (403,892; 46.3% increase), Durham (228,330; 22.1% increase), Greensboro (269,666; 20.4% increase), Wilmington (269,666), and Winston-Salem (229,617; 23.6% increase); few counties lost residents. The aging population in the state is steadily growing, but the proportion of those  $\geq 65$  years compare to national estimates of about 13%. By race and ethnicity, non-Hispanic Whites in 2011 comprised

65.3% of the state's population (13% increase), 21.5% Black (18% increase), 8.4% Hispanic or Latino (100% increase), 1.3% Native American, 2.2% Asian; 2.2% reported two or more races (U.S. Census Bureau, 2012). About 53% of North Carolinians are female, a figure that is comparable to the national average. The state is a popular destination for older adult retirees who wish to relocate to areas with access to medical centers, universities, a multi-generational population, a wide range of leisure pursuits, and a temperate climate.

North Carolina (N.C.) is geographically defined by mountain (west), piedmont (central), and coastal (east) regions with metropolitan, suburban, and rural communities dispersed across the state. The steady growth of urban and suburban communities has reduced the number of rural and farming communities and impacted employment in communities that lack a diverse economic opportunity base. Despite population growth and economic development in some sectors of the state, loss of jobs in agriculture, fishing, industry, and textiles and furniture manufacturing has created economic hardship across the state. Growth in agribusiness, manufacturing, and pharmaceuticals has increased demand for a workforce with more advanced knowledge and technical skill.

The per capita income of North Carolinians for 2010 was \$24,745 (national average, \$27,334) and the median household income was \$45,570 (national average, \$51,914; U.S. Census Bureau, 2012). The poverty level in the state exceeds the national average. Approximately 15.5% of North Carolinians live below the poverty level compared to 13.8% nationally. Transient workers and a large migrant population in the

agriculture and service industries often have unstable economic and living circumstances that contribute to significant health and social needs.

In a report on the health status of North Carolinians from the North Carolina Institute of Medicine (NC-IOM), there were improvements noted in infant mortality, cardiovascular disease mortality, and tobacco use among youth (NC-IOM, 2011). However, North Carolina ranks 35<sup>th</sup> in overall health status. Relevant North Carolina health indicators that ranked in the bottom one-third of all states were obesity, smoking, premature death, infant mortality, and cardiovascular disease (NC-IOM, 2011). Social determinants of health such as poverty, unemployment and underemployment, limited years or quality of education, inadequate or no health insurance, lack of transportation, substandard housing, and barriers to high quality health care impacts the health of many North Carolinians.

### **Study Setting**

This study was conducted at a large academic medical center located in central North Carolina that is part of a private, not-for-profit health system. The medical center is a 943-bed teaching hospital and regional emergency and Level 1 trauma center. In addition to the medical center there are two community hospitals and 25 outpatient clinics in the health system. Medical center physicians and nurse practitioners provide clinical services to a Veteran's Affairs Medical Center and a continuing care retirement community outpatient clinic and inpatient unit. As a designated tertiary/quaternary care setting, the medical center admits acutely ill and medically complex patients from across the state and nationally. Some patients transfer to the medical center from community

hospitals for advanced medical or surgical treatment. Thus, the inpatient population is diverse and the acuity level and complexity of care for many patients is high.

For fiscal year 2010, the medical center had 40,647 inpatient encounters, 1,101,741 outpatient visits, 68,646 emergency department visits, and 725 patients transported by an emergency transport system using medically-staffed helicopters for urgent patient transfers. In 2010, the hospital system provided \$258.2 million in charity health care and other services to low income people. Approximately 20% of medical center patients receive Medicaid funding. The medical center and affiliating university is distinguished by nationally-renowned geriatric expertise in nursing, medicine, psychology, social work, physical therapy, anthropology, and other disciplines. This expertise draws older adults to the region for health care from affiliates within the medical center health system and to retirement communities that provide independent and supportive living arrangements and health care.

The medical center was well-suited for this study because of its size, location, draw of patients from across the state and nationally, and diverse demographic and health profile of its service population with representation of social determinants of health. This setting was equipped with the technological resources to conduct this study and served as a real-life laboratory to describe frailty in hospitalized adults.

### **Data Access**

Study data was retrieved from the EMR. An exploratory study sample was first constructed using a proprietary data query tool developed for the health system for clinical research, administrative monitoring, and quality improvement projects. The data

query tool is a software program to access the Data Storage Repository (DSR) of archived health system clinical data that are integrated for retrospective studies (Horvath et al., 2011). The DSR included electronic medical record data for inpatient and outpatient encounters in the health system since 1996 and contains over 4 million records. Using the data query tool, potential cases are randomly assigned a unique identifier (UID) that links to health system data including the Patient Identification Key, medical record number (MRN), and hospital admission encounter number. These identifiers assured that the correct patient encounter was included in the study sample. The UID is not linked with or documented in the EMR. In a deidentified dataset, only the UID is retained for data management.

Initial query of the DSR required submission of a Review Preparatory to Research (RPR) form to the Office of Information and Technology and the medical center Institutional Review Board (IRB). The RPR described the study and data to be extracted from the DSR using the data query system prior to submission of a study protocol to the IRB (Horvath et al., 2011). The RPR for this study was approved on January 14, 2011 by the medical center IRB (Record Number 4454). After approval of the RPR, preliminary data exploration was conducted. Table 4 illustrates the query procedure and development of the final analytic sample using the data query tool procedures.

The data query tool searched the DSR with delimitations defined by the inclusion criteria. This query yielded 690 patients with one or more independent hospital encounters during the study time frame. Almost half (48.7%,  $n = 336$ ) and the remainder had two or more hospital encounters. Table 5 displays frequency data on the number of

independent hospital encounters for the 690 patients in the sample. About 2% ( $n = 24$ ) had between nine and eleven hospital encounters.

Table 4

## Data Query to Construct the Study Sample Using Study Inclusion Criteria

Health System: DSR	Health System Data Storage Repository (DSR) of all Patient Encounters Health System: One academic medical center, two community hospitals, 25 outpatient, community, and school-based clinics Total number of independent encounters in the DSR: 4 million+
<b>Data Query with Delimiters</b>	
Exploratory Sample  $N=690$	Setting: one academic medical center Study Time Frame: June 1, 2010 through August 31, 2011 Age: 55 years and older Admitting Service: General Medicine, Cardiology, Orthopedics Admission included an overnight stay  Total number of independent medical center encounters: 690 (number of patients with one hospital encounter: 336) (number of patients with two or more hospital encounters: 354)
Final Analytic Sample  $N = 278$	Selection of One Independent Hospital Encounter per Patient with Complete Data for Inclusion Criteria and Four Biomarkers: 281  Exclusion criteria (cancer diagnosis with active treatment); less than 24 hours without overnight stay

Patients with two or more encounters were examined. One encounter was selected based on the study inclusion and exclusion criteria. The final analytic sample included 278 independent hospital encounters. Following submission and approval of the medical center IRB protocol, additional clinical data was retrieved from the EMR using an online search tool. All data retrieved for this study were accessed from EMR documentation pertaining to health status on admission.

Table 5

Frequency Count of Independent Hospital Encounters for the Sample ( $N = 690$ )

Count	Frequency	%	Cumulative Frequency	Cumulative %
1	336	48.70	336	48.70
2	177	25.65	513	74.35
3	89	12.90	602	87.25
4	45	6.52	647	93.77
5	19	2.75	666	96.52
6	9	1.30	675	97.83
7	6	0.87	681	98.70
8	4	0.58	685	99.28
9	2	0.29	687	99.57
10	2	0.29	689	99.86
11	1	0.14	690	100.00

### **Demographic, Biologic, Psychologic, Social, and Spiritual Domains**

#### **Demographic Data**

Demographic variables included preadmission living location (home, other), admitting service (general medicine, cardiology, orthopedics), occupation (professional, technical/service, self-employed, unemployed, retired, disabled), number of hospital encounters during the study time frame (count), discharge disposition (home [self-care, home health], extended care [skilled nursing facility, rehabilitation facility, another hospital], hospice [home visits, inpatient facility], expired), length of stay (number of

days from date of admission to date of discharge), and 30-day readmission to study medical center. Data on admissions to other hospitals was not available.

### **Biologic Domain**

Age was recorded as the numeric age on the date of admission based on year of birth. Gender (female, male) and race/ethnicity (White, Black, American Indian, Asian, Hispanic/Latino, Other) were recorded as nominal variables. Race/ethnicity was also coded as categorical variable, 0 = Minority (Black, American Indian, Asian, Hispanic/Latino, or Other), 1 = White. Weight was recorded in kilograms and height was recorded in centimeters. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared ( $\text{kg}/\text{m}^2$ ). Other biologic variables were categorical and scored as 1 = Yes, 0 = No. these included unplanned weight loss of 15 pounds or more in the past 6 months, recent unplanned weight loss, poor appetite, acute pain, weakness, fatigue, urinary incontinence, pressure ulcer or vascular ulcer, infection, falls admission diagnosis, history of falls, fever reported prior to admission or recorded on admission, activities of daily living (ADL) assistance needed prior to admission, ADL assistive device used prior to admission, unplanned surgery during hospitalization, and physician diagnosis or documentation of failure-to-thrive or frail on admission.

Comorbidity was defined as the count of all medical diagnoses which conform to the ICD-9/10 code that were listed on the physician admission or emergency department admission forms or other relevant documentation. Each diagnosis category included selected ICD-9/10 medical diagnoses pertinent to chronic inflammation or frailty based on empirical evidence in the scientific literature. The 12 medical diagnosis categories

were identified based evidence for their high prevalence in the study population age group and association with symptoms that require self-management, functional impairment, chronic inflammation, and/or frailty.

The 12 diagnostic categories and corresponding ICD9/10 medical diagnoses (in parentheses) were: (a) hypertension; (b) cardiovascular disease (coronary artery disease, angina, myocardial infarction, peripheral vascular disease, deep vein thrombosis/pulmonary embolism, heart failure, atrial fibrillation); (c) liver disease (cirrhosis, hepatitis); (d) neurological disease (cerebral vascular attack [CVA], transient ischemic attack [TIA], Parkinson's disease); (e) pulmonary disease (chronic obstructive pulmonary disease (COPD), bronchitis, emphysema, asthma, pneumonia); (f) endocrine conditions (diabetes mellitus, hypothyroidism); (g) cancer, except dermatologic, and not under active treatment; (h) cognition (dementia, any type, Alzheimer's disease, delirium); (i) psychological disorders (depression, anxiety, bipolar); (j) musculoskeletal disorders (osteoarthritis/degenerative joint disease, osteoporosis/osteopenia, hip fracture); (k) inflammatory or autoimmune disease (Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis, HIV/AIDS); and (l) ocular disease (cataracts [corrected or uncorrected], glaucoma, macular degeneration, retinopathy, blind). These medical diagnoses were coded as categorical variables where 1 = Yes, documented on admission, and 0 = No, not documented on admission. Medical diagnoses were identified from admission documentation and interdisciplinary notes. The 12 medical diagnosis categories were also coded as categorical variables based on EMR documentation of the presence of at least one of the medical diagnoses listed for that category. Only one

medical diagnosis documented in the EMR for that diagnosis category was required to be present for that category to be coded as 1 = Yes, or 0 = No.

Laboratory data was available for four plasma biomarkers: CRP or hs-CRP, albumin level, hemoglobin concentration, and WBC count. The variable used in this study was the abnormal flag, defined as a laboratory value that is higher or lower than the established reference range, accounting for gender differences when applicable. The abnormal flag was a categorical variable that was coded as 1 = Yes, abnormal flag present and 0 = No, abnormal flag not present. Biomarker reference ranges coincide with reference ranges recommended by the World Health Organization (hemoglobin), American Heart Association (CRP, hs-CRP), and the American Society of Clinical Pathology (all). CRP and hs-CRP are the same analyte and were examined as one categorical variable. Table 6 provides laboratory reference ranges and testing equipment used at the medical center.

Medications were recorded as the count of all prescription and non-prescription medications taken on a routine basis documented on admission, and the count of persons whose medication count was  $\geq 5$  based on definitions of polypharmacy and its adverse effects for frailty, disability, hospitalization, mortality, and falls (Gnjidic et al., 2012). The medication count  $\geq 5$  was coded as 1 = Yes, 0 = No. For sample description, ten medication categories related to inflammation, physical function, cognition, and/or frailty were identified: (a) statin; (b) non-steroidal anti-inflammatory drug (NSAID), aspirin (ASA); (c) corticosteroid, immunosuppressant; (d) angiotensin converting enzyme-inhibitor (ACE-I), angiotensin receptor blocker (ARB); (e) hormone therapy (estrogen,

progesterone, testosterone); (f) opioid; (g) benzodiazepine; (h) diuretic; (i) calcium, vitamin D, bisphosphonate; and (j) beta-blocker. The name or number of individual medications was not recorded. The medication category was scored as 1 = Yes, if the admission medication list included any medications classified by that category, or 0 = No, if the admission list did not include any such medications.

Table 6

## Laboratory Assay Equipment\* and Reference Ranges for Plasma Biomarkers

Biomarker	Reference Range	Laboratory Value for Abnormal Flag
CRP, high**	Low risk: < .10 mg/dL Intermediate risk: .10 - .30 mg/dL  High risk: > .30 mg/dL	Abnormal flag, >0.30 mg/dL
hs-CRP, high	< .6 pg/dL	Abnormal flag, >.6 pg/dL
Albumin, low	3.5-4.8 g/dL	Abnormal flag, <3.6 g/dL
Hemoglobin, low	Women: 12.0 - 15.5 g/dL  Men: 13.7 - 17.3 g/dL	Abnormal flag, <12.0 g/dL  Abnormal flag, < 13.7 g/dL
WBC, high or low	3.2 - 9.8 x 10 <sup>9</sup> cfu	Abnormal flag , >9.8 or <3.2x 10 <sup>9</sup> cfu

\*Laboratory assay equipment: CRP and hs-CRP (Beckman Cyncron Systems Neon Infrared Particle immunoassay rate methodology); albumin (Beckman-Colter Unicel DXC 600-800, Broumresol Purple (dcp) Timetest Endpoint); WBC and hemoglobin (Electronic Impedence Differential Lysis Flourescent Flow Cytometry and Colorimetric Measurement).

\*\*Reference range established for risk levels by the Centers for Disease Control and Prevention and the American Heart Association: <1 mg/L; low risk, 1-3mg/L; intermediate risk; > 3mg/L, high risk (Pearson et al., 2003).

The Braden Scale is a multidimensional pressure ulcer risk assessment tool that is commonly used in practice with established validity and reliability (Anthony, Parboteeah, Saleh, & Papanikolaou, 2008; Beeson et al., 2010; Bergstrom & Braden, 2002; Bergstrom, Braden, Kemp, Champagne, & Ruby, 1998; Bergstrom, Braden, Laguzza, &

Holman, 1987; Bergstrom, Demuth, & Braden, 1987; S. J. Brown, 2004; Pancorbo-Hidalgo, Garcia-Fernandez, Medina, & Alvarez-Nieto, 2006). The Braden Scale score is a composite measure of biologic vulnerability associated with risk for pressure ulcer development. The Braden Scale has six subscales: sensory perception, moisture, activity, mobility, nutrition, and friction and shearing). Subscales are rated on a three or four point Likert-type scale and summed (range, 6 to 23). Lower scores indicate higher risk for pressure ulcer development. The Braden Scale score was defined as a continuous variable computed as the sum of the six subscales.

### **Psychologic Domain**

Psychologic variables included memory problems (self-report or provider assessment), abnormal mental status (provider assessment), cognition problems (ICD-9/10 admission diagnosis of dementia [any type], Alzheimer's disease, delirium), ICD-9/10 admission diagnosis of depression, chronic pain (self-report), sleep problems (self-report, use of continuous positive airway pressure [CPAP] at night), and current tobacco use (self-report). These variables were coded as categorical variables.

### **Social Domain**

Social domain variables were living arrangement (live alone), marital status (married or not married/single [single, separated, divorced, widowed]), caregiver concerns (pertained to the nature of the patient's condition and post-hospital care issues, based on self-report or documentation of concerns by care providers), and a high risk indicator found on the nursing admission assessment form, "older, disabled, lives alone." These variables were coded as categorical variables.

### **Spiritual Domain**

The spiritual domain included documentation of patient request for a clergy visit on the nursing admission assessment or one or more clergy visits documented during hospitalization if the visit note indicated patient request. This variable was coded as a categorical variable.

### **Frailty Components, Indicator Variables, and Measurement**

The 14 frailty components were defined by 26 indicator variables that included: (a) Nutrition (unplanned weight loss of 15 pounds in the six months prior to admission, recent unplanned weight loss, poor appetite, BMI <18.5 kg/m<sup>2</sup>, BMI >30 kg/m<sup>2</sup>); (b) Fatigue (fatigue, tired, lack of endurance or difficulty sleeping, use of CPAP (continuous positive airway pressure) for sleep); (c) Weakness; (d) Chronic pain; (e) Dyspnea; (f) Falls (admission diagnosis, history of falls); (g) Vision (cataracts [corrected, uncorrected], glaucoma, macular degeneration, diabetic retinopathy, blind); (h) Cognition (mental status abnormal, memory problem, dementia [any type, Alzheimer's disease], delirium); (i) Depression (ICD-9/10 code); (j) Social support (live alone, single, caregiver concerns, older adult, disabled, and lives alone); (k) CRP or hs-CRP (abnormal flag, high); (l) Albumin (abnormal flag, low); (m) Hemoglobin (abnormal flag, low); and (n) WBC count (abnormal flag, high or low). Table 7 lists the 14 frailty components and the corresponding 26 frailty indicator variables.

Table 7

The 14 Frailty Components and 26 Indicator Variables ( $N = 278$ )

	Frailty Component *	Indicator Variable
1.	Nutrition (5)	Unplanned weight loss of 15 pounds, past 6 months Recent unplanned weight loss Poor appetite BMI < 18.5 kg/m <sup>2</sup> BMI > 30 kg/m <sup>2</sup>
2.	Weakness	Weakness reported or demonstrated
3.	Fatigue (2)	Fatigue, tired, poor endurance Sleep problems, use of CPAP at night
4.	Chronic pain	Chronic pain
5.	Dyspnea	Dyspnea, shortness of breath
6.	Falls (2)	Falls admission diagnosis History of falls
7.	Vision	Ocular diagnosis: cataracts (corrected, uncorrected), glaucoma, macular degeneration, retinopathy, blind
8.	Cognition (4)	Memory problem Mental status abnormal Dementia diagnosis Delirium
9.	Depression	Depression diagnosis
10.	Social support (4)	Lives alone Single (single, separated, divorced, widowed) Caregiver concerns Older adult, disabled, and lives alone
11..	CRP or hs-CRP	Plasma CRP or hs-CRP, abnormal flag, high
12.	Albumin	Plasma albumin, abnormal flag, low
13.	Hemoglobin	Plasma hemoglobin, abnormal flag, low
14.	WBC count	Plasma WBC, abnormal flag, abnormal-high or low

\*Number of indicator variables for the frailty component, if more than one, noted in parentheses.

### Characterization and Scoring of Frailty

Frailty was represented by 14 components that consisted of 26 evidence-based indicator variables. All frailty components and indicator variables were defined as categorical, binary variables, where “Yes = 1” indicated that an indicator variable or

frailty component was present and “No = 0” indicated that an indicator variable or frailty component was not present. Each frailty components was scored as one point. The presence of one indicator variable for a frailty component was sufficient to score the frailty component as present, or 1 = Yes. A Frailty Score was derived from the sum count of the frailty components (not indicator variables) for a ranged of 0 to 14 points. Lower scores suggest lower risk for frailty or level of frailty or not frail and higher scores suggest increased risk for frailty or higher level of frailty.

### **Study Outcome Variables**

The study outcome variables were hospital length of stay and 30-day hospital readmission. Length of stay was defined as a count of the number of days from the date of admission through the date of discharge. Thirty-day readmission was defined as admission to the study medical center within 30-days of the discharge date. Data for length of stay and 30-day readmission was retrieved from the EMR using the data query tool for data abstraction from the DSR. The reason for readmission was not recorded.

### **Validity**

Validity refers to the extent to which a measure represents what it is designed to measure. Face validity assesses the face value and may be based on expert opinion, strength of scientific evidence, and relevance of component elements. Construct validity is the extent to which a measure satisfactorily represents all relevant facets of a construct. Face and construct validity was met by using prior research, theory, and expert opinion from researchers and clinicians in geriatric medicine, nursing, sociology, physical therapy, palliative care, and biomedical diagnostics to inform the conceptualization and

operational definition of frailty and the 14 frailty components. Construct validity was addressed in the data collection process by review of multiple records in the EMR to confirm the presence or absence of a frailty component indicator variable. Data collection was conducted by study personnel with verification of all records and re-verification of selected records by variable or by case by the student researcher to ensure data accuracy, validity, completeness, and consistency.

The 14 frailty components and 26 indicator variables were selected based on theory, prior research and empirical evidence from several frailty definitions and conceptualizations: the frailty phenotype, deficits accumulation, multidimensional frailty, comprehensive geriatric assessment, inflammation, and the study BPSS-Stress conceptual model. Three frailty components were based on the frailty phenotype (nutrition, weakness, fatigue) and two components were based on modified versions which included cognition and depression (Ávila-Funes, et al., 2009, 2011; Bandeen-Roche et al., 2006; Bartali et al., 2006; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; T. E. Seeman et al., 2001; Stenholm et al., 2008; Villareal et al., 2006; Xue et al., 2008). Evidence for the frailty components and indicator variables is cited in Table 8.

Table 8

Evidence for the Frailty Components and Indicator Variables

	Frailty Component	Indicator Variables	References
1.	Nutrition	Weight loss of 15 pounds, past 6 months Unplanned weight loss	Abellan van Kan et al., 2010; Bales & Ritchie, 2002; Bandeen-Roche et al., 2006; Bartali et al., 2006; Blaum et al., 2005; Chin A Paw et al., 2003; Cooper et al., 2012; Cornali et al., 2005; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Jarosz & Bellar,

Table 8. (Cont.)

	Frailty Component	Indicator Variables	References
1.	Nutrition (cont.)	Poor appetite BMI < 18.5 kg/m <sup>2</sup> BMI > 30 kg/m <sup>2</sup>	2009; Jeejeebhoy, 2012; Kinney, 2004; National Institute on Aging, 1991; Stenholm et al., 2008; Stiffler, Finley, Midha, & Wilber, 2013
2.	Falls	Falls admission diagnosis  Self-report, History of falls	Cesari et al., 2004; Ensrud et al., 2008, 2009; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Gill, Allore, et al., 2010; Mahoney, 1998; Nowak & Hubbard, 2009; Rubenstein, 2006; Samper-Ternent et al., 2012; Speciale et al., 2004; Speechley & Tinetti, 1999
3.	Weakness	Self-report, Health provider assessment	Abellan van Kan et al., 2010; Cesari et al., 2004; K. E. Covinsky et al., 2003; Fried, Tangen, et al., 2001; Forti et al., 2012; Hardy & Studenski, 2008; Leng et al., 2007; Manty et al., 2012; Marzetti & Leeuwenburgh, 2006; National Institute on Aging, 1991; Reuben et al., 2002, 2003; Stiffler et al., 2013; Toye et al., 2006; Walke et al., 2004; Whitson et al., 2009
4.	Vision	ICD-9/10 diagnosis of ocular disease: cataracts (corrected, uncorrected), glaucoma, macular degeneration, retinopathy, blind	Cesari, et al., 2004; C. C. Chen et al., 2011; Hardy & Studenski, 2008; Klein, Klein, et al., 2003; Klein et al., 2005; Knudtson et al., 2009; Studenski et al., 2004; Whitson, et al., 2009; Whitson, Ansah, et al., 2010
5.	Dyspnea	Self-report, Health provider assessment	Brinkley et al., 2009; S. S. Chang et al., 2011; Galizia et al., 2011; Guralnik et al., 2000; Hardy & Studenski, 2008; Schwartz & Weiss, 1993; Walke et al., 2004; Whitson et al., 2009
6.	Cognition	Memory problems: Self-report, Provider assessment  Mental status abnormal: Self-report, Provider assessment  Dementia: ICD-9/10 diagnosis of dementia, any type, Alzheimer's disease	Ávila-Funes et al., 2009, 2011; Cesari et al., 2003a; 2003b; M. G. Cole et al., 2009; M. Cole, McCusker, Dendukuri, & Han, 2003; Ford et al., 2010; Fitzpatrick, Stier, et al., 2004; Gill et al., 2006; Inouye, Schlesinger, & Lydon, 1999; Juster et al., 2010; Kiely et al., 2009; Mitniski et al., 2011; Quinlan et al., 2011; Ranjit, Diez-Roux, Shea, Cushman, Seeman, et al., 2007; Rigney, 2010; Rockwood et al., 2004; Rothman et al., 2008; Sands et al., 2003; Whitson et al., 2009; Whitson, Ansah, et al., 2010a

Table 8. (Cont.)

	Frailty Component	Indicator Variables	References
6.	Cognition (cont.)	Delirium: Self-report, Provider assessment	
7.	Depression	ICD-9/10 diagnosis of depression, current or history	K. E. Covinsky et al., 1997, 2003, 2010; Lenz et al., 2005; McEwen, 2003b; Mezuk et al., 2011; Ní Mhaoláin et al., 2012; Ostir et al., 2004; Rothman et al., 2008; T. E. Seeman et al., 2001; Simonsick et al., 1998
8.	Fatigue	Fatigue, tired, poor endurance: Self-report, Provider assessment Sleep problems: Self-report, Provider assessment, CPAP at night for sleep	Abellan van Kan et al., 2010; Avlund et al., 2006, 2007; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Hardy & Studenski, 2008, 2010; Inouye et al., 2007; Jeejeebhoy, 2012; Manty et al., 2012; National Institute on Aging, 1991; Schultz-Larsen & Avlund, 2006; Toye et al., 2006; Vas Fragoso et al., 2009; Walke et al., 2004; Whitson et al., 2009
9.	Chronic pain	Self-report	Blyth et al., 2008; K. E. Covinsky et al., 2009; Davis et al., 2011; Hardy & Studenski, 2008; Maxwell et al., 2008; Shega et al., 2012; Walke et al., 2004; Whitson et al., 2009
10.	Social support	Live alone Single Caregiver concerns Older adult, disabled, live alone	Aggar et al., 2011; Andrew et al., 2008; Bilotta et al., 2010; Chappell, 1991; Fugate Woods et al., 2005; Gleib et al., 2007; Landi et al., 2004; Loucks et al., 2006; McEwen, 1993; Newsom & Schultz, 1996; Rockwood et al., 2005; Schultz & Williamson, 1993; T. E. Seeman et al., 1997; T. E. Seeman & McEwen, 1996; von Känel et al., 2006; Woo et al., 2005
11.	Biomarkers CRP, hs-CRP	Abnormal flag, high	Arques et al., 2008; Avlund et al., 2007; Bandeen-Roche et al., 2009; Barzilay et al., 2007; Cesari et al., 2003a, 2003b, 2004; Chaves et al., 2005; Corti et al., 1994; K. E. Covinsky et al., 2002; De Martinis et al., 2006; Don & Kaysen, 2004; Ferrucci et al., 1999, 2002; Ford et al., 2006; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Glaser & Kiecolt-Glaser, 2005; Gleib et al., 2007; Gruenwald et al., 2006; Kanapuru & Ershler, 2009; Kiecolt-Glaser et al., 2003; Leng et al., 2002, 2009; Leng, Xue, Huang, Ferrucci, et al., 2005; Leng, Xue, Huang, Semba, et al., 2005; Loucks, Berkman, et al., 2006; Loucks, Sullivan, et al., 2006; McEwen, 2008; National Institute on Aging, 2004; Nielson et al., 2007; Oda & Kawai, 2010; Penninx et al., 2004; Puts et al., 2011; Reuben et al., 2003; Szanton et al., 2005; Taaffe et al., 2000; Tak et al., 2009; Taylor, Lehman, Kiefe, & Seeman, 2006; Visser et al., 1999; Walston et al., 2002; Yao et al., 2011
12.	Albumin	Abnormal flag, low	
13.	Hemoglobin	Abnormal flag, low	
14.	WBC count	Abnormal flag, abnormal-high or low	

### **Data Acquisition and Data Entry**

Data retrieval from the EMR was conducted by research personnel listed in the IRB protocol. Questions about coding were adjudicated by the study investigators and recorded in a notebook to ensure ongoing consistent and accurate data retrieval and coding. Data was initially entered into a Microsoft Excel<sup>®</sup> spreadsheet. To ensure data entry accuracy, consistency, and completeness, the student researcher verified 100 % of data collection forms with data in the EMR. Variables that demonstrated a higher rate of coding error were examined and coding errors were corrected and missing data was retrieved from the EMR. After data cleaning, the Microsoft Excel<sup>®</sup> data file was imported into an SPSS (Version 20, IBM, Chicago, IL) file for analysis. SAS (Version 9.3, SAS Institute, Cary, NC) was used to convert certain variables yielded from the online data query from text format into numeric data. These variables with numeric data were then imported into the SPSS data file.

### **Data Analysis**

#### **Sample Description, Data Distribution, and Missing Data**

Descriptive statistics were computed for quantitative categorical and continuous measures. Data were examined for dispersion and variance. For categorical variables, measures of dispersion or central tendency included mean ( $M$ ), median, and mode. For continuous variables, measures of variance included range (minimum, maximum), standard deviation ( $SD$ ), 95% confidence interval (95%  $CI$ ), interquartile range ( $IQR$ ), normality, kurtosis, and skew. Categorical data were represented by frequency (count), number ( $n$ ), and percent (%). For continuous data, frequencies and interquartile ranges

(IQR) were examined. Histograms with superimposed normal curve, normal probability P-P plots and Q-Q plots data were examined in comparison to expected values. The P-P plots, Q-Q plots, and Stem-and-Leaf plots were visually inspected for normality, distribution pattern, and outliers. Kurtosis and skew were examined to assess normality. Kurtosis is demonstrated by a distribution of scores at the tails as leptokurtic (pointy) or platykurtic (flattened). Skew is a measure of symmetry. Abnormal skew shows an asymmetrical clustering of scores at one end of a tail. In a normal distribution, the value of skew and kurtosis are 0. For sample sizes  $> 200$ , visual inspection of the shape of the distribution and kurtosis and skew can be sufficient in assessing normality. The Kolmogorov-Smirnov test and Shapiro-Wilk tests were also performed to assess normality. Significant tests ( $p < .05$ ) suggest that the data are significantly different from a normal distribution. Missing data was managed by visually inspecting the SPSS data file for blank fields and reviewing the EMR to retrieve data. There was no missing data in the study sample (Field, 2009; Huck, 2008; Tabachnik & Fidell, 2007).

### **Power Analysis**

Power analysis was conducted for linear regression to determine adequacy of the sample size, the probability level for statistical significance, and the ability of statistical tests to detect an effect. The power of a test is the probability that a given test will find an effect assuming that one exists in the population (Field, 2009). A level of power typically recommended is .80 and an alpha of .05 (Field, 2009; Huck, 2008). Power analysis was performed using NQuery (Version 3.19.2013.20310, Microsoft Corporation, Seattle, WA). Power was calculated with alpha set at .05, for 20 predictor variables and sample

size of 278. The level of power was .99 indicating the ability to detect a large effect size. The study sample size was adequate for multiple linear and logistic regression analyses.

### **Analysis**

Descriptive statistics were computed for demographic, biologic, psychologic, social-spiritual variables. Data analysis procedures included bivariate tests of association using Pearson and Spearman's rho correlations and bivariate linear regressions to examine relationships between demographic, biologic, psychologic, social, and spiritual health status variables and the 14 frailty components and the Frailty Score. Several multiple linear regression procedures were used to examine for significant associations between candidate predictor variables and the Frailty Score to determine optimal model fit for a parsimonious set of predictor variables. Logistic regression was performed to assess if the Frailty Score predicted 30-day hospital readmission. Simple linear regression was conducted to assess if the Frailty Score predicted  $\log^{10}$  transformed length of stay. Conventional procedures for data verification, data examination prior to analyses, data transformation, and for performing statistical tests were followed (Field, 2009; Huck, 2008; Tabachnik & Fidell, 2007).

Statistical analyses were conducted using SAS (Version 9.3, SAS Institute, Cary, NC) and SPSS (Version 20, IBM, Inc., Chicago, IL). Two-tailed statistical tests were performed with level of significance set at .05 for all analyses unless otherwise specified.

## Research Questions

### Research Question 1

*What is the proportion of each of the 14 frailty components in hospitalized adults 55 years of age and older?*

The number ( $n$ ) and percent (%) of patients in the sample who score 1 on each of the 14 frailty components was portrayed using descriptive statistics. Frequency distributions, histograms with normal curves, normal probability P-P plots, Q-Q plots, Stem-and-Leaf plots, and whisker box plots were analyzed to assess data characteristics.

### Research Question 2

*What is the level of frailty in the sample of hospitalized adults, based on level of frailty, or the Frailty Score that ranges from 0 to 14?*

The Frailty Score was examined for frequency, dispersion and variance. Measures of central tendency included the mean ( $M$ ), median, and mode. Measures of dispersion and variance included the range (minimum, maximum), standard deviation, 95% confidence interval, interquartile range (IQR), normality, kurtosis and skew. Frequency distributions, histograms with normal curves and probability P-P plots and Q-Q plots, Stem-and-Leaf plots, and IQRs were visually examined. Outliers were checked for data entry errors and their impact on central tendency and dispersion.

### Research Question 3

*What are the relationships between demographic, biological, psychological, and social-spiritual health status variables and each of the 14 frailty components?*

Bivariate tests of association were conducted using Pearson and Spearman's rho correlations. Bivariate associations were assessed between each of the 14 frailty components and each of the 20 demographic, biological, psychological, social-spiritual categorical and quantitative continuous candidate predictor variables. Fourteen categorical frailty components and the 14 categorical candidate predictor variables were: preadmission location (home, other), gender (female), race/ethnicity (Minority [Black, American Indian, Asian, Hispanic-Latino, Other]), current tobacco use, acute pain on admission, urinary incontinence on admission, pressure ulcer or vascular ulcer on admission, fever prior to or present, infection on admission, ADL assistance prior to admission, ADL device used, unplanned surgery during hospitalization, physician diagnosis or documentation on admission of failure-to-thrive or frail, and clergy visit during hospitalization. The Pearson *Chi-square* ( $X^2$ ) test statistic and *p* value was reported for the 14 frailty components and the 14 quantitative categorical candidate predictor variables. The Fisher's exact test *p* value and Pearson *Chi-square* ( $X^2$ ) test statistic was reported when data were unequally distributed among the cells or the expected value in a cell was less than five.

Spearman's rho correlations were computed for the 14 frailty components and six quantitative continuous candidate predictor variables. The six continuous predictor variables were age in years on date of admission, BMI, Braden Scale raw score, comorbidity count, total medication count, and number of hospital encounters during the study time frame. Spearman's rho  $r^2$  and *p* value were reported.

**Research Question 4**

*What are the relationships between the demographic, biological, psychological, and social-spiritual health status variables and the level of frailty, or Frailty Score, that ranges from 0 to 14?*

Multiple linear regression was conducted to assess for linear relationships between the 20 categorical and continuous candidate predictor variables and the Frailty Score. The standardized  $\beta$  weights,  $t$  values, degrees of freedom ( $df$ ), sample size,  $F$  statistic, adjusted  $R^2$ , and  $p$  value were reported. Seven statistically significant predictor variables were identified. To assess the model and to determine each of the predictor variables remained in the model, multiple linear regression was performed with the seven significant predictor variables and the Frailty Score. The standardized  $\beta$  weights,  $t$  values, degrees of freedom ( $df$ ), sample size,  $F$  statistic, adjusted  $R^2$ , and  $p$  value were reported. Further statistical analyses were undertaken to explore linear relationships. First, bivariate linear regression was conducted for each of the 20 categorical and quantitative continuous candidate predictor variables and the Frailty Score. Candidate predictor variables with significant correlation coefficients were identified. Multiple linear regression was next performed using the ENTER method where all 20 candidate predictor variables were included in the regression model. The standardized  $\beta$  weights,  $t$  values, degrees of freedom ( $df$ ) and sample size, the  $F$  statistic, the adjusted  $R^2$ , and  $p$  value. Then, multiple regression was performed using the STEPWISE method where only candidate predictor variables with  $p$  values  $< .10$  in the bivariate linear regression were included in the regression model. Selecting predictor variables based on a more

liberal alpha of .10 permitted including variables that may demonstrate significant associations when analyzed in different combinations with other predictors in accordance with the STEPWISE method. The standardized  $\beta$  weights,  $t$  values, degrees of freedom ( $df$ ) and sample size,  $F$  statistic, adjusted  $R^2$ , and  $p$  value were reported. The results from the regression models were compared and summarized.

Assumptions for linear regression when using continuous variables were checked for normal distribution, linearity, independence and multicollinearity, homogeneity of variance, homoscedasticity, and normal distribution of residuals. Multicollinearity was assessed by examining the variance inflation factor (VIF), tolerance, and eigenvalues. Cook's Distance was examined for overall influence of outliers. Cook's Distance values  $> 1$  would be of concern. The Durbin-Watson test identified if residuals were correlated. Values range from 0 to 4, where 2 indicate non-correlation, and values  $< 3$  or  $> 1$  are of concern. Sample distribution and outliers were inspected using normal probability P-P plots, Q-Q plots, Stem-and-Leaf plots, whisker plots, and histograms with a superimposed normal curve. The influence of outliers was analyzed to determine the need for data transformation. Residuals were examined to assess model fit and influential cases. Only 5% of standardized residuals should be greater than +1.96, only 1% should be greater than 2.58, and cases close to 3 should be closely inspected. Cases  $>3$  would be cause for concern. Histograms of standardized residuals with a superimposed normal curve were examined. Data transformation was not performed for any of the candidate predictor variables.

**Research Question 5**

*What is the relationship between level of frailty, or Frailty Score, and length of hospital stay?*

Simple linear regression was performed to examine the relationship between the Frailty Score (theoretic range, 0-14) as the predictor variable and length of stay as the outcome continuous variable. Linear regression assumptions as described above were assessed. F statistic was used to examine the model fit. The adjusted  $R^2$  was also examined. The  $R^2$  is the partial correlation between the outcome variable and each of the predictor variables, which range from -1 to +1. A positive  $R^2$  indicates that as the predictor variable increases, the likelihood of the outcome increases. Similarly, as a predictor variable decreases, the likelihood of the outcome decreases. A significant variable with a low adjusted  $R^2$  contributes a small amount in explaining variance in the outcome. The total model and variable adjusted  $R^2$ , degrees of freedom ( $df$ ), sample size,  $F$  statistic, and  $p$  value were reported. Length of stay was significantly non-normally distributed. A new variable for length of stay was computed using  $\log^{10}$  transformation. The standardized  $\beta$  weight,  $t$  value, degrees of freedom ( $df$ ) and sample size, the  $F$  statistic, adjusted  $R^2$ , and  $p$  value were reported.

**Research Question 6**

*What is the relationship between level of frailty, or Frailty Score, and 30-day hospital readmission?*

The relationship between the Frailty Score (range, 0–14) and 30-day medical center readmission was examined using logistic regression. The Frailty Score was the

predictor variable and 30-day readmission was the binary outcome variable where 1 = readmitted and 0 = not readmitted. Regression assumptions described above were assessed. The logistic regression model was assessed by examining the log-likelihood of the observed and predicted values of predictor variables to assess the fit of the model. The log-likelihood statistic is an indicator of the amount of unexplained variance that exists after the model has been fitted. Larger values indicate poor model fit since this indicates more unexplained observations. The Hosmer and Lemeshow tests were examined to evaluate goodness-of-fit of a logistic regression model and the *Chi*-square test statistic, degrees of freedom, and p value reported. The Wald test statistic, which is based on a *Chi*-square distribution, was used to determine if the standardized  $\beta$  coefficient for a predictor variable was significantly different from 0. A standardized  $\beta$  coefficient that is significantly different from 0 suggests that the predictor is making a significant contribution to the outcome. The odds ratio was computed but was not applicable since the logistic regression model was not statistically significant (Field, 2009; Tabachnik & Fidell, 2007).

### **Protection of Human Subjects**

In accordance with medical center policy, all Protected Health Information (PHI) data was removed from the data file. The UID generated for each hospital encounter was retained in the data file. The UID is not recorded in the EMR and cannot be linked to study data. A list with the Patient Identification Key, MRN, hospitalization encounter number, and the UID was secured in the locked office of the Principal Investigator. The Patient Identification Key, MRN, and hospitalization encounter number were not

available to the dissertation student or study personnel. IRB approval for the study protocol was obtained from the medical center and from the university.

### **Study Limitations**

This cross-sectional, retrospective, descriptive study to characterize frailty in hospitalized adults had several limitations. The study design was based on observational data derived from the EMR that was recorded for clinical purposes. Some empirically-validated frailty criteria such as performance measures and assessment measures for domains of the BPSS-Stress conceptual model were not available in the EMR. Although suitable proxies were identified, some of the indicator variables for the frailty components were not the most salient based on prior research, theory, and the study BPSS-Stress conceptual model.

Accuracy and completeness of data available in the EMR would be expected to vary depending on health care provider expertise and experience, time constraints, and attention to the past medical history that may or may not be pertinent to the immediate reason for hospitalization. Secondary data analysis is unavoidably associated with risk for incomplete, inaccurate, and/or missing data. To reduce this risk, clinical data retrieved from the EMR was cross-validated with documentation from nursing and medicine and other various health care providers. All data collection forms and the analytic dataset underwent verification by study investigators to ensure completeness, accuracy, and consistency in documentation. Coding questions were adjudicated by study investigators and decisions logged in a notebook to ensure consistent documentation. Previously completed data collection forms were audited, the EMR reviewed, and corrections made.

The study population consisted of admissions to a large academic medical center with access to medical and surgical specialists, diagnostic procedures, and treatments not typically available at smaller, non-academic hospitals. In this study, one hospital encounter was included in the dataset. Only health status on admission documented in the EMR was examined. Frailty is a dynamic process that follows a fluctuating course with potential for stabilization and recovery or precipitous or progressive decline that may lead to poor health outcomes. Thus, frailty was characterized at an arbitrary, static moment in time, providing a snapshot of the health status of acutely ill adults on admission. It was outside the scope of this study to examine frailty during hospitalization, at discharge, and after discharge. There is substantial evidence that hospitalization is independently associated with high risk for untoward, potentially preventable events such as falls, injury, infection, delirium, pain, medication side effects, pressure ulcers, depression, new functional decline and mobility impairment. These untoward events increase risk for the inception of frailty or accelerate its progression and severity. Frailty status on admission therefore may provide information about vulnerability to adverse events but exposure during hospitalization to risk may significantly alter level of frailty. This may be clinically important in patients who have few frailty components or lower level of frailty on admission but experience one or more significant adverse events during hospitalization that quickly changes their risk status and increases their vulnerability to deleterious consequences to subsequent adverse events.

### **Chapter Summary**

Frailty was characterized in hospitalized adults 55 years of age and older admitted to the general medicine, cardiology, and orthopedic services at a large academic medical center from June 1, 2010 through August 31, 2011. Fourteen frailty components were operationalized to characterize frailty based on prior research and empirical evidence, theory, the study conceptual model, and BPSS health status variables available in the EMR. The sample consisted of 278 independent hospital admissions. Descriptive statistics, tests of association and correlation, bivariate and multiple linear regression, and logistic regression were performed to examine associations between the 14 frailty components and 20 BPSS health status variables and if level of frailty, or the Frailty Score, predicted hospital length of stay and 30-day hospital readmission.

## **CHAPTER IV**

### **RESULTS**

Findings from this descriptive, cross-sectional, retrospective study are reported in this chapter. This study characterized frailty in hospitalized adults 55 years of age and older admitted to the general medicine, cardiology, or orthopedic service in one large academic medical center and determined if level of frailty, represented as a Frailty Score, predicted hospital length of stay and 30-day hospital readmission.

#### **Sampling Method and Population**

A preliminary study sample was constructed using data query procedures described in Chapter III. Sociodemographic data were retrieved from electronic medical records (EMR) archived in the health system Data Storage Repository. The preliminary sample yielded 690 independent hospital encounters (admissions) during the 15-month study time frame. Individual patients in the preliminary sample had between one and eleven hospital encounters. One hospital encounter per patient was selected based on study inclusion criteria yielding 281 independent hospital encounters. Three patients were excluded based on an admission diagnosis of non-dermatologic cancer with active treatment. Thus, the final analytic sample was 278 independent hospital encounters.

#### **Sample**

Sample characteristics for the demographic and BPSS domains delineated in the study conceptual model are presented in Table 9. The mean age was 70 years (range, 55-

98 years) with adequate age representation in the sample. Slightly over half were female, half were single (single, separated, divorced, widowed), about two-thirds were White. There were no encounters where race/ethnicity was identified as Hispanic/Latino. Most admissions were from home and one-fifth was from a skilled nursing facility, rehabilitation center, or another hospital. Twenty percent of the sample lived alone. Most were retired and one out of five was disabled.

Table 9

Sample Characteristics for Demographic, Biologic, Psychologic, and Social-Spiritual Domains ( $N = 278$ )\*

Variable	Number (%) or Mean ( <i>SD</i> ), range	
Demographic Domain		
Preadmission location	Home	224 (80.6)
	Other (extended care, rehabilitation facility, other hospital)	54 (15.4)
Discharge location	Home (self-care) or home health	150 (54.0)
	Skilled nursing facility, rehabilitation facility, another hospital	105 (37.8)
	Hospice (home or medical facility)	10 (3.6)
	Expired	13 (4.7)
Admitting service	General medicine	194 (69.8)
	Cardiology	55 (19.8)
	Orthopedics	29 (10.4)
Marital status	Married	142 (51.1)
	Widowed	61 (21.9)
	Single	43 (15.5)
	Divorced	26 (9.4)
	Separated	6 (2.2)
Occupational status	Employed	28 (10.2)
	Retired	179 (64.4)
	Disabled	58 (20.9)
	Unemployed	13 (4.7)

Table 9. (Cont.)

Variable		Number (%) or Mean ( <i>SD</i> ), range
Demographic Domain (cont.)		
Number of hospitalizations	During 15-month study time frame	1.56 (0.93), 1-8
Length of stay	—	9.92 (9.6), 1-72
30-day hospital readmission	—	33 (11.9)
Biologic Domain		
Gender	Female	146 (52.5)
	Male	132 (47.5)
Age	In years on admission date	70.2 (10.3), 55-98
Age tertiles	55-64 years	100 (36.0)
	65-74 years	84 (30.2)
	75 years and older	94 (33.8)
Race/Ethnicity	White (Caucasian)	178 (64.0)
	Black (African American)	92 (33.1)
	American Indian	2 (0.7)
	Asian	2 (0.7)
	Other	4 (1.4)
	Hispanic/Latino	0
Comorbidity count	Sum count of ICD 9/10 medical diagnoses on admission	13 (4.56), 1-26
Comorbidity categories ( <i>n</i> = 12)	Hypertension	229 (82.4)
	Cardiovascular disease	192 (69.1)
	Pulmonary disease	93 (33.5)
	Liver disease	25 (8.6)
	Musculoskeletal disorder	152 (54.7)
	Endocrine disease	158 (56.8)
	Cognition	92 (33.1)
	Neurological disease	58 (20.9)
	Renal disease	146 (52.5)
	Inflammatory/autoimmune	42 (15.1)
	Psychiatric disorder	114 (41)
	Cancer	63 (22.7)
	Vision disorders	95 (34.2)
Infection on admission	—	184 (66.2)
Unplanned surgery	—	95 (34.2)
Failure-to-thrive or frail	ICD 9/10 diagnosis on admission or MD documentation	21 (7.6)

Table 9. (Cont.)

Variable		Number (%) or Mean ( <i>SD</i> ), range
Biologic Domain (cont.)		
Fever	Prior to or on admission	100 (36)
Acute pain	—	196 (70.5)
Weakness	—	227 (81.7)
Fatigue	—	249 (89.6)
Urinary incontinence	—	66 (23.7)
Dyspnea, shortness of breath	—	104 (37.4)
Pressure or vascular ulcer	—	81 (29.1)
Braden Scale score	Sum of six subscales, range 6-23	17.89 (3.3), 9-23
Medication count	Sum count of prescription and non-prescription medications taken on routine basis	11.87 (5.2), 0-31
Medication count $\geq 5$	Number of patients with medication count $\geq 5$	264 (95)
Medication categories ( <i>n</i> = 10)	Statin	126 (45.3)
	Nonsteroidal, aspirin	181 (65.1)
	Corticosteroid, immunosuppressant	59 (21.2)
	ACE-Inhibitor, ACE-Receptor Blocker	135 (48.6)
	Sex hormone	18 (6.5)
	Opioid	137 (49.3)
	Benzodiazepine	57 (20.5)
	Diuretic	143 (51.4)
	Calcium, vitamin D, bisphosphonate	92 (33.1)
	Beta blocker	142 (51.1)
BMI	—	28.6 (7.64), 13-65
BMI $>25$ kg/m <sup>2</sup>	—	183 (65.8)
Plasma Biomarkers*		
CRP or hs-CRP	Abnormal flag, high	246 (88.5)
Albumin	Abnormal flag, low	258 (92.8)
	Plasma value	2.58 (0.7), 1-4
Hemoglobin	Abnormal flag, low	10.44 (1.8), 6-16
	Plasma value	267 (96)
WBC count	Abnormal flag, high or low	206 (74.1)
	Plasma value	11.70 (4.7), 1-29

\*Refer to Table 6 for abnormal flag laboratory value

Table 9. (Cont.)

Variable	Electronic Medical Record	Number (%) or Mean (SD), range
Psychologic Domain		
Tobacco, current use	—	45 (16.2)
Chronic pain	—	71 (25.5)
Difficulty sleeping	Self-report, use of CPAP at night	152 (54.7)
Mental status abnormal	—	173 (62.2)
Memory problems	—	71 (25.5)
Depression	ICD 9/10 diagnosis on admission	97 (34.7)
Delirium	ICD 9/10 diagnosis on admission	70 (25.2)
Dementia	ICD 9/10 diagnosis on admission	25 (9)
Social-Spiritual Domain		
Live alone	—	56 (20.1)
ADL assistance needed	—	183 (66.8)
ADL device used	—	175 (62.9)
Caregiver concern	Carer concerns about patient health status, post-hospital care needs, resources, finances	119 (42.8)
Clergy visit	Requested on admission, recorded during hospitalization	65 (23.4)

Multiple morbidity was high. The mean number of medical diagnosis listed on admission was 13 (range, 0–26). To ensure accuracy, data for chronic medical conditions were retrieved from consultation reports or primary care visit notes since all pertinent medical conditions may not listed in admission documentation. Acute infection was present in two-thirds on admission and over one-third had a fever prior to or on admission. Symptom burden was high. Acute pain was reported in almost three-quarters and chronic pain in one-quarter of the sample. Fatigue, weakness, urinary incontinence, abnormal mental status, delirium, difficulty sleeping, depression, and vision problems were commonly reported on admission, however, fatigue was the most ubiquitous. About two-thirds were over-weight or obese, defined as BMI > 25 kg/m<sup>2</sup>. Pressure ulcer or

vascular ulcers were present on admission in 29% and was one common reason for unplanned surgery during hospitalization. The primary reason for admission for about 10% of the sample was related to falls and almost one-third had a history of falls. The mean Braden Scale score was 18 (range, 9–23); lower Braden Scale scores are predictive of higher risk for pressure ulcer development. The mean number of prescription and non-prescription medications taken on a routine basis documented on admission was 12 (range, 0–31). About 8% ( $n = 21$ ) had a physician diagnosis or notation of failure-to-thrive or frailty. Abnormal flags for the biomarkers associated with inflammation, chronic stress, and frailty (CRP or hs-CRP, albumin, hemoglobin, WBC count) were highly prevalent. Abnormal flags for three of four biomarkers were present in over 89% of the sample.

Almost three-quarters of the sample were admitted to the general medicine service however about one-third had unplanned surgery during hospitalization typically as a result of failed medical treatment. The most common surgical procedures were incision and drainage of abscesses, treatment of post-surgical incisions, fistulas, hematomas, or pressure or vascular ulcers, repair or removal of joint replacement hardware, and limb amputation or revision of a prior amputation. No major cardiac, orthopedic, gastrointestinal, or neurologic surgical procedures were documented. During hospitalization, unit transfers including intensive care occurred but these data were not recorded since frailty status on admission was the focus of the study.

Discharge disposition for more than half of the sample was home (self-care or with home health services), extended care (skilled nursing or rehabilitation facility), or

another hospital. Less than 5% were discharged to hospice care provided in a medical facility. Five percent died during hospitalization. Almost two-thirds (62.9%) had one hospital encounter during the 15-month study time frame, however, four patients had five hospital encounters and one patient had eight. Extreme outliers accounted for less than 2% of the sample. Mean length of stay was 9.92 days (*SD*, 9.96, range, 1–72). Thirty-three patients (12%) were readmitted within 30-days of hospital discharge.

### **Frailty Score**

The Frailty Score consisted of the sum of 14 frailty components. All frailty components and indicator variables were operationalized as categorical, where 1 = Yes, present on admission, and 0 = No, not present on admission. Twenty-six indicator variables that best represented the study conceptual model domains defined the 14 frailty components. Most frailty components were defined by one indicator variable. Five frailty components were defined by more than one indicator variable and included Nutrition (five), Fatigue (two), Falls (two), Cognition (four), and Social Support (four). Only one indicator variable needed to be present to score one point for the frailty component. Frailty components coded as one point were summed to compute the Frailty Score. Lower Frailty Scores suggested lower risk for frailty or not frail and higher Frailty Scores suggested increased risk for or greater level of frailty. The frequency count and percent for the 26 categorical indicator variables for the frailty components for the BPSS domains are presented in Table 10.

Table 10

Frequency and Percent of the 26 Categorical Indicator Variables ( $N = 278$ )

Indicator Variables	<i>n</i> (%)
Biologic Domain	
1. Unplanned weight loss, 15 pounds, past 6 months	87 (31.3)
2. Recent unplanned weight loss	103 (37.1)
3. Poor appetite	158 (56.8)
4. BMI < 18.5 kg/m <sup>2</sup>	20 (7.2)
5. BMI > 30 kg/m <sup>2</sup>	103 (37.1)
6. Fatigue	249 (89.6)
7. Weakness	227 (81.7)
8. Dyspnea, shortness of breath	104 (37.4)
9. Falls admission diagnosis	26 (9.4)
10. Falls history	75 (27)
11. Vision (cataracts, glaucoma, macular degeneration, retinopathy, blind)	95 (34.2)
12. Plasma CRP or hs-CRP, abnormal flag, high	246 (88.5)
13. Plasma albumin, abnormal flag, low	258 (92.8)
14. Plasma hemoglobin, abnormal flag, low	267 (96)
15. Plasma WBC, abnormal flag, abnormal-high or low	206 (74.1)
Psychologic Domain	
16. Chronic pain	173 (62.2)
17. Sleep problems, use of CPAP at night	152 (54.7)
18. Delirium	70 (25.2)
19. Memory problem	71 (25.5)
20. Mental status abnormal	71 (25.5)
21. Dementia	25 (9)
22. Depression	97 (34.9)
Social-Spiritual Domain	
23. Live alone	56 (20.1)
24. Older adult, disabled, live alone	51 (18.3)
25. Single (single, separated, divorced, widowed)	136 (48.9)
26. Caregiver concerns	119 (42.8)

### Research Question 1

*What is the proportion of each of the 14 frailty components in hospitalized adults 55 years of age and older?*

The 14 frailty components were Nutrition, Weakness, Fatigue, Chronic Pain, Dyspnea, Falls, Vision, Cognition, Depression, Social Support, and abnormal flags for four plasma biomarkers: CRP or hs-CRP (high), Albumin (low), Hemoglobin (low), and WBC count (abnormal, high or low). Table 11 reports the frequency count and percent of the 14 frailty components identified in the sample.

Table 11

Frequency Count and Percent of the 14 Frailty Components in the Sample ( $N = 278$ )

Frailty Component	<i>n</i> (%)
1. Nutrition	227 (81.7)
2. Weakness	227 (81.7)
3. Fatigue	249 (89.6)
4. Chronic Pain	173 (62.2)
5. Dyspnea	104 (37.4)
6. Falls	80 (28.8)
7. Vision	95 (34.2)
8. Cognition	92 (33.1)
9. Depression	97 (34.9)
10. Social Support	190 (68.3)
11. CRP or hs-CRP, abnormal flag (high)	246 (88.5)
12. Albumin, abnormal flag (low)	258 (92.8)
13. Hemoglobin, abnormal flag (low)	267 (96)
14. WBC count, abnormal flag (abnormal, high or low)	206 (74.1)

Fatigue, Weakness, and Nutrition were documented in over 80% of the sample.

Chronic Pain and Social Support issues were documented in about two-thirds of the

sample, and Dyspnea, Falls, Cognition, Depression, and Vision problems were documented in slightly over one-third of the sample. The prevalence of abnormal flags for all four biomarkers was high. Two-thirds of the sample had an abnormal flag for all four biomarkers whereas only 1% had one abnormal flag. Low abnormal flag for Hemoglobin and Albumin was almost universal. About three-quarters had an abnormal flag for WBC count (all but two were high).

### **Research Question 2**

*What is the level of frailty in the sample, based on a Frailty Score of 0 to 14?*

The mean Frailty Score was 9.03 (*SD*, 1.98, range, 2-13) and the median and mode were 9. The frequency distribution of Frailty Scores indicated that only 4.3% ( $n = 6$ ) had a Frailty Score from two to five and 12% ( $n = 32$ ) had a Frailty Score of 12 or 13. The Frailty Score was examined according to procedures described in Chapter 3. The Frailty Score was modestly skewed (-.472) indicating that most scores fell to the right of the mean. The data distribution was modestly peaked with little variance indicating slight kurtosis (.269). The Kolmogorov-Smirnov and Shapiro-Wilk tests were significant indicating a non-normal distribution. Visual inspection of the data indicated that the data distribution and degree of non-normality did not warrant transformation.

### **Research Question 3**

*What are the relationships between demographic, biological, psychological, and social-spiritual health status variables and each of the 14 frailty components?*

Tests for association between 20 categorical and quantitative continuous candidate predictor variables representing demographic, BPSS domains and the 14

categorical frailty components were analyzed using procedures described in Chapter 3. Tests of association were performed to examine relationships between the 14 categorical candidate predictor variables and each of the 14 categorical frailty components. The Pearson *Chi*-square or Fisher's Exact test were performed. The Pearson *Chi*-square test statistic and *p* value and, if indicated, the Fisher's Exact test *p* value were examined. The Fisher's Exact test was reported when the expected frequency in each cell was less than five. When the Fisher's Exact test *p* value was reported, the Pearson *Chi*-square test statistic was documented with the *p* value.

Of the 14 candidate predictor variables, eleven were coded as 1 = Yes, present on admission, or 0 = No, not present on admission. The 11 variables included ADL assistance needed, ADL device used, acute pain, pressure or vascular ulcer, infection, fever, current tobacco use, urinary incontinence, unplanned surgery during hospitalization, clergy visit during hospitalization, and physician diagnosis or documentation of failure-to-thrive or frail on admission. Three demographic variables were coded as follows: gender (1 = female; 0 = male), race/ethnicity (1 = Minority [Black, American Indian, Asian, Hispanic/Latino, Other]; 0 = Caucasian), and pre-admission location (1 = home; 0 = other). There was no Hispanic/Latino representation in this study sample.

For the six quantitative continuous candidate predictor variables, Spearman's rho was computed to examine associations between each candidate predictor variable and each of the 14 categorical frailty components. The six continuous candidate predictor

variables were age, BMI, comorbidity count, medication count, Braden Scale score, and number of hospital admissions during the study time frame.

Table 12 reports the *Chi*-square test statistic and Fisher's exact test *p* value for significant categorical candidate predictor variables and the 14 frailty components. The frailty component, Social Support, was significantly associated with the most categorical predictor variables (seven): race/ethnicity (Minority), gender (female), preadmission location (home), ADL assistance needed, pressure or vascular ulcer, urinary incontinence, and clergy visit. The abnormal flag for Fatigue (low) and Hemoglobin (low) were not significantly associated with any candidate predictor variables. Depression was significantly associated only with race/ethnicity (Minority). Nutrition was significantly associated with preadmission location (home) and current tobacco use. Dyspnea was significantly associated with infection and unplanned surgery. Weakness was significantly associated with ADL assistance needed, ADL device used, pressure or vascular ulcer, and urinary incontinence. Chronic Pain was significantly associated with ADL assistance needed, ADL device used, acute pain, and physician diagnosis or documentation of failure-to-thrive or frailty on admission. Falls were significantly associated with ADL assistance needed, ADL device used, current tobacco use, and urinary incontinence. Vision was significantly associated with race/ethnicity (Minority), female gender, and pressure or vascular ulcer. Cognition was significantly associated with preadmission location (home), ADL assistance needed, and urinary incontinence.

Table 12

Tests for Association for 14 Categorical Candidate Predictor Variables for the Demographic, Biologic, Psychologic, and Social-Spiritual Domains and 14 Categorical Frailty Components ( $N = 278$ )

Frailty Component	Variables													
	Race	Gender	Pre-admit location	ADL assist	ADL device	Acute pain	Pressure Ulcer	Infection	Tobacco use	Incont.	Fever	Surgery	Clergy visit	Failure-to-thrive or frail
Nutrition	—	—	5.352 .019*	—	—	—	—	—	4.889 .033*	—	—	—	—	—
Weakness	—	—	—	19.663 .000*	—	—	7.185 .006*	—	—	6.701 .010*	—	—	—	—
Fatigue	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Chronic Pain	—	—	—	6.966 .009*	17.003 .000**	57.815 .000**	—	—	—	—	—	—	—	8.070 .008*
Dyspnea	—	—	—	—	—	—	—	9.614 .003*	—	—	—	9.094 .003*	—	—
Falls	—	—	—	8.339 .005*	12.023 .001**	—	—	—	4.736 .047*	6.215 .019*	—	—	—	—
Vision	—	5.319 .023*	—	—	—	—	5.361 .026*	—	—	—	—	—	—	—
Cognition	—	—	17.893 .000**	9.450 .002*	—	—	—	—	—	36.464 .000	—	—	—	—
Depression	5.436 .026*	—	—	—	—	—	—	—	—	—	—	—	—	—
Social Support	11.561 .003*	4.501 .039*	10.823 .001**	10.516 .002*	—	—	14.983 .000**	—	—	5.720 .022*	—	—	4.013 .049*	—
CRP, hs-CRP	—	—	—	—	—	—	—	8.135 .009*	—	—	6.500 .011*	5.530 .018*	—	—
Albumin	—	—	—	12.297 .001**	4.867 .032*	—	—	4.323 .049	—	—	—	—	—	—
Hemoglobin	—	—	—	—	—	—	—	—	—	—	—	—	—	—
WBC count	—	—	4.291 .039*	9.005 .004*	—	—	4.421 .036*	7.807 .006*	—	5.209 .024*	—	11.220 .001**	—	—

§Only statistically significant variables reported.

Pearson *Chi*-square test statistic and Fisher's Exact test *p* value reported for all variables

\*Statistical significance,  $p < .05$  (2-tailed)

\*\*Statistical significance,  $p < .001$  level (2-tailed)

Albumin abnormal flag (low) was significantly associated with Weakness, Vision, Social Support, WBC count abnormal flag (abnormal, high or low). Unplanned surgery was significantly associated with Dyspnea, CRP or hs-CRP abnormal flag (high), and WBC count abnormal flag (abnormal, high or low).

Categorical candidate predictor variables significantly associated with the 14 frailty components were examined. ADL assistance needed was significantly associated with the most frailty components (seven): Weakness, Chronic Pain, Falls, Cognition, Social Support, Albumin abnormal flag (low), and WBC count abnormal flag (abnormal, high or low). Urinary incontinence was significantly associated with five frailty components: Weakness, Falls, Cognition, Social Support, and WBC count abnormal flag (abnormal, high or low). Race/ethnicity (Minority) was significantly associated with three frailty components: Vision, Depression, and Social Support. Candidate predictor variables significantly associated with one or two frailty components were acute pain (Chronic Pain), fever (CRP or hs-CRP abnormal flag, high), physician (MD) documentation of failure-to-thrive or frail on admission (Chronic Pain), clergy visit (Social Support), current tobacco use (Nutrition, Falls), and female gender (Vision, Social Support). Use of an ADL device was significantly associated with Chronic Pain, Falls, and Albumin abnormal flag (low). There were no significant patterns of association between frailty components and any individual or cluster of candidate predictor variables.

Table 13 reports significant Spearman's rho correlation  $r_s$  and  $p$  values for the quantitative continuous predictor variables and 14 categorical frailty components. Vision was significantly associated with the most continuous predictor variables (four): age,

comorbidity count, lower Braden Scale score, and number of hospital admissions during the 15 month study time frame. Nutrition and Dyspnea were significantly associated with BMI. Weakness was significantly associated with three: age, BMI, and Braden Scale score. Depression was significantly associated with higher comorbidity count and higher medication count. Dyspnea was associated with BMI and comorbidity count. Falls was significantly associated with BMI and comorbidity count, and number of hospital encounters. Cognition was significantly associated with age and lower Braden Scale score. Chronic Pain was significantly associated with BMI and Social Support was significantly associated with lower Braden Scale score. Fatigue was not significantly associated with any predictor variables. Three biomarkers, CRP or hs-CRP (abnormal flag, high), low albumin (abnormal flag, low), and WBC count (abnormal flag, high or low), were significantly associated with lower Braden Scale scores. Hemoglobin abnormal flag (low) was significantly associated with medication count.

Table 13

Tests for Association between 14 Quantitative Continuous Candidate Predictor Variables and each of the 14 Categorical Frailty Components: Significant Spearman's  $\rho$  Point Biserial Correlation  $r_s$  and  $p$  Value<sup>§</sup> ( $N = 278$ )

	Age	BMI	Comorbidity count	Medication count	Braden Scale score	Number of hospitalizations
Nutrition	—	.188** .000	—	—	—	—
Weakness	.128* .034	.119* .048	—	—	-.269** .000	—
Fatigue	—	—	—	—	—	—
Chronic pain	—	.147* .014	—	—	—	—

Table 13. (Cont.)

	Age	BMI	Comorbidity count	Medication count	Braden Scale score	Number of hospitalizations
Dyspnea	—	.146*	.162**	—	—	—
		.015	.007			
Falls	.252**	—	.181**	—	-.145*	—
	.000		.002		.015	
Vision	.233**	—	.250**	—	-.143*	.140*
	.000		.000		.017	.020
Cognition	.223**	—	—	—	-.374**	—
	.000				.000	
Depression	—	—	.172**	.202**	—	—
			.004	.000		
CRP, hs-CRP	—	—	—	—	-.136*	—
					.023	
Albumin	—	—	—	—	-.184**	—
					.002	
Hemoglobin	—	—	—	.129*	—	—
				.031		
WBC count	.160**	—	—	—	-.331**	—
	.008				.000	
Social support	—	—	—	—	-.201**	--
					.001	

§Only statistically significant values reported

\*Spearman's rho  $r_s$ , and  $p < .05$  level (2-tailed)

\*\*Spearman's rho  $r_s$ , and  $p < .01$  level (2-tailed)

Candidate predictor variables significantly associated with the most frailty components were lower Braden Scale score and age. Lower Braden Scale scores were significantly associated with nine frailty components: Weakness, Falls, Vision, Cognition, CRP or hs-CRP (abnormal flag, high), Albumin (abnormal flag, low), and WBC count (abnormal flag, high or low), and Social Support. Age was significantly associated with seven frailty components: Weakness, Falls, Vision, Cognition, and WBC (abnormal flag, high or low). BMI was significantly associated with Nutrition, Weakness, Chronic Pain, and Dyspnea. Comorbidity count was significantly associated with Dyspnea, Falls, Vision, and Depression.

The four biomarkers were not significantly associated with many categorical or continuous variables. Three of the four biomarkers were significantly associated with infection on admission. WBC count abnormal flag (abnormal) was significantly associated with the most variables (five): pressure ulcer or vascular ulcer, infection on admission, urinary incontinence, ADL assistance needed, and unplanned surgery during hospitalization. CRP or hs-CRP abnormal flag, high) was significantly associated with infection and fever prior to or on admission. Albumin abnormal flag (low) was significantly associated with ADL assistance needed, ADL device used, and infection. Hemoglobin abnormal flag (low) was not significantly associated with any variables.

#### **Research Question 4**

*What are the relationships between the demographic, biological, psychological, and social-spiritual health status variables and level of frailty, represented as the Frailty Score that ranges from 0 to 14?*

The Frailty Score and candidate predictor variables were examined for regression model assumptions as described in Chapter III. Tests for multicollinearity between candidate predictor variables were acceptable indicating there were no strong linear relationships that could bias the regression models (Field, 2009; T. A. Lang & Secic, 2006). First, tests for association were performed between the 20 quantitative categorical and continuous candidate predictor variables and the Frailty Score. The Pearson *Chi*-square test statistic and *p* value or the Fisher's Exact test and *p* value were computed for the categorical predictor variables and Spearman's rho  $r_s$  and *p* value were computed for the continuous candidate predictor variables and the continuous dependent variable, the

Frailty Score. This analysis yielded 12 statistically significant predictor variables. Significant predictor variables were age, female gender, Braden Scale score, current tobacco use, pressure ulcer or vascular ulcer, urinary incontinence, ADL assistance needed, ADL device used, medication count, comorbidity count, preadmission location (home), and number of hospitalizations during the 15-month study time frame. Predictor variables that were not statistically significant were race/ethnicity (Minority), BMI, acute pain, fever, infection, unplanned surgery, clergy visit, and physician (MD) diagnosis or documentation of failure-to-thrive or frail on admission.

#### **Multiple Linear Regression for Candidate Predictor Variables and Frailty Score**

Multiple linear regression was conducted for the 20 candidate predictor variables and Frailty Score ( $N = 278$ ). The multiple linear regression, or model 1, was statistically significant. Seven statistically significant predictor variables were identified in the regression model: older age, lower Braden Scale score, current tobacco use, acute pain, ADL assistance needed, urinary incontinence, and higher comorbidity count. Regression coefficients are reported in Table 14. Model 1 explained 26% of the variance in the Frailty Score. Predictor variables with the highest standardized  $\beta$  coefficients were current tobacco use, ADL assistance needed, and lower Braden Scale score. Collinearity test statistics were acceptable.

Next, multiple linear regression was performed using the seven statistically significant predictor variables identified above and the Frailty Score to test model fit for a more parsimonious model. The findings from this multiple linear regression indicate that all predictor variables remained statistically significant. Predictor variables with the

highest standardized  $\beta$  coefficients were Braden Scale score, ADL assistance needed, current tobacco use, and higher comorbidity count. Collinearity statistics were acceptable. The regression standardized  $\beta$  coefficients, 95% *CI*, and *p* values are reported in Table 15.

Table 14

Multiple Regression  $\beta$  Coefficients for the Frailty Score and 20 Categorical and Quantitative Continuous Candidate Predictor Variables ( $N = 278$ )

Model <sup>a</sup>	Standardized Coefficients			95% Confidence Interval for $\beta$	
	$\beta$	<i>t</i>	<i>Sig.</i>	Lower Bound	Upper Bound
Constant		3.830	.000	2.636	8.215
<b>Age in years on admission</b>	<b>.141</b>	<b>2.223</b>	<b>.027*</b>	<b>.003</b>	<b>.051</b>
Gender (female)	.097	1.725	.086	-.055	.828
Race/ethnicity (Minority)	-.017	-.304	.762	-.520	.381
BMI	.083	1.436	.152	-.008	.051
<b>Braden Scale Score</b>	<b>-.154</b>	<b>-2.341</b>	<b>.020*</b>	<b>-.171</b>	<b>-.015</b>
Total number of encounters	.050	.910	.364	-.125	.339
<b>Tobacco use, current</b>	<b>.199</b>	<b>3.662</b>	<b>.000**</b>	<b>.496</b>	<b>1.650</b>
Pressure ulcer or vascular ulcer	.094	1.610	.109	-.092	.912
<b>Acute pain</b>	<b>.109</b>	<b>2.014</b>	<b>.045*</b>	<b>.011</b>	<b>.933</b>
<b>ADL assistance needed</b>	<b>.155</b>	<b>2.381</b>	<b>.018*</b>	<b>.112</b>	<b>1.181</b>
ADL device used	.013	.214	.831	-.448	.557
Clergy visit during hospitalization	.049	.895	.371	-.272	.726
Pre-admission location (home)	.001	.011	.991	-.598	.596
<b>Urinary incontinence</b>	<b>.136</b>	<b>2.291</b>	<b>.023*</b>	<b>.089</b>	<b>1.178</b>
Medication count, higher	.055	.878	.381	-.026	.088
<b>Comorbidity count, higher</b>	<b>.140</b>	<b>2.288</b>	<b>.023*</b>	<b>.009</b>	<b>.144</b>
Unplanned surgery	-.013	-.247	.805	-.503	.391
Failure-to-thrive or frail per MD diagnosis or documentation	.004	.065	.984	-.813	.869
Fever prior to or recorded on admission	.053	.971	.333	-.226	.664
Infection	.005	.080	.936	-.449	.487

Adjusted  $R^2 = .260$ ,  $df(20, 257)$ ,  $F = 5.865$ ,  $df(20, 257)$ ,  $p = .000$ , Durbin-Watson = 1.851

<sup>a</sup> Dependent variable: Frailty Score

\*Statistical significance,  $p < .05$  level (2-tailed)

Table 15

Multiple Regression Coefficients for Frailty Score and Seven Significant Predictor Variables ( $N = 278$ )<sup>a</sup>

Model <sup>a</sup>	Standardized Coefficients			95% Confidence Interval for $\beta$	
	$\beta$	$t$	Sig.	Lower Bound	Upper Bound
Constant		9.376	.000	6.744	10.329
Age in years on admission	.116	2.134	.034*	.021	.528
Braden Scale score	-.201	-3.274	.001**	-.194	-.048
Tobacco use, current	.177	3.339	.001**	.391	1.516
Acute pain	.115	2.171	.003**	.046	.951
ADL assistance needed	.194	3.397	.001**	.341	1.281
Urinary incontinence	.134	2.293	.023*	.088	1.157
Comorbidity count, higher	.166	3.109	.002**	.026	.118

Adjusted  $R^2 = .254$ ,  $df(7, 270)$ ,  $F = 14.483$ ,  $df(7, 270)$ ,  $p = .000$ , Durbin-Watson = 1.809

<sup>a</sup> Dependent variable: Frailty Score

\*Statistical significance,  $p < .05$  level (2-tailed)

\*\*Statistical significance,  $p < .01$  level (2-tailed)

### Multiple Linear Regression Using ENTER and STEPWISE Method

To further explore conceptual and operational constructs of frailty, a second set of multiple linear regression models, or model 2, were performed using the ENTER and STEPWISE method. First, bivariate linear regression was performed for each of the 20 candidate predictor variables and the Frailty Score. Level of significance for candidate predictor variables was set at  $p < .10$  to provide slightly more liberal inclusion criteria (Field, 2009; Tabachnik & Fidell, 2007). Bivariate regression identified 14 statistically significant predictor variables: age in years on date of admission, female gender, comorbidity count, medication count, pressure ulcer or vascular ulcer, Braden Scale score, infection, urinary incontinence, acute pain, current tobacco use, ADL assistance needed, ADL assistive device used, preadmission location (home), and number of

hospital encounters during the study time frame. The other six candidate predictor variables were not statistically significant and not included in subsequent analyses. Table 16 displays bivariate linear regression standardized  $\beta$  coefficients and  $p$  values for the Frailty Score and the 20 candidate predictor variables.

Table 16

Bivariate Linear Regression Coefficients for the Frailty Score and 20 Candidate Predictor Variables ( $N = 278$ )

Variable	$B$	Regression Coefficient (Sig., $p < .10$ )
Biologic Variables		
Constant	.000	
1. Age in years on admission	.212	$p = .000$
2. Gender (female)	.154	$p = .010$
3. Comorbidity count	.242	$p = .000$
4. Medication count	.182	$p = .002$
5. Pressure ulcer or vascular ulcer	.253	$p = .000$
6. Braden Scale score	-.375	$p = .000$
7. Infection	.104	$p = .084$
8. Urinary incontinence	.247	$p = .000$
9. Acute pain	.106	$p = .077$
Psychological Variables		
10. Tobacco use, current	.141	$p = .019$
Social Variables		
11. ADL assistance needed	.337	$p = .000$
12. ADL device used	.234	$p = .000$

Table 16. (Cont.)

Variable	<i>B</i>	Regression Coefficient (Sig., $p < .10$ )
Demographic Variables		
13. Preadmission location (home)	.212	$p = .000$
14. Total number of encounters	.117	$p = .051$
		Regression Coefficient Not Sig.
15. BMI	.044	$p = .460$
16. Race/ethnicity (Minority)	.075	$p = .214$
17. Unplanned surgery	.000	$p = .996$
18. Fever prior to or on admission	.022	$p = .717$
19. Failure-to-thrive or frail per MD diagnosis or documentation	.064	$p = .287$
20. Clergy visit during hospitalization	.081	$p = .178$

<sup>a</sup> Dependent variable: Frailty Score

Next, multiple linear regression was performed using the ENTER method for the 14 statistically significant candidate predictor variables identified from bivariate linear regression and the Frailty Score. Seven statistically significant variables were identified: female gender, higher comorbidity count, current tobacco use, acute pain, urinary incontinence, ADL assistance needed, and lower Braden Scale score. Predictor variables with the highest standardized  $\beta$  coefficients were current tobacco use, ADL assistance needed, and higher comorbidity count. The regression model was statistically significant. Collinearity statistics were acceptable. Table 17 reports the standardized  $\beta$  coefficients, 95% *CI*, and  $p$  values for the multiple regression.

Table 17

Multiple Regression Coefficients for Frailty Score and 14 Significant Predictor Variables using ENTER Method ( $N = 278$ )

Model <sup>a</sup>	Standardized Coefficients			95% CI for $\beta$	
	$\beta$	$t$	Sig.	Lower Bound	Upper Bound
Constant		4.863	.000	3.719	8.781
Age in years	.107	1.812	.071	-.002	.043
<b>Gender (female)</b>	<b>.112</b>	<b>2.054</b>	<b>.041*</b>	<b>.019</b>	<b>.872</b>
Medication count, higher	.056	.925	.356	-.024	.066
<b>Comorbidity count, higher</b>	<b>.149</b>	<b>2.506</b>	<b>.013*</b>	<b>.014</b>	<b>.116</b>
Pressure or vascular ulcer	.096	1.680	.094	-.072	.906
<b>Tobacco use, current</b>	<b>.185</b>	<b>3.472</b>	<b>.001**</b>	<b>.431</b>	<b>1.561</b>
<b>Acute pain</b>	<b>.112</b>	<b>2.110</b>	<b>.036*</b>	<b>.003</b>	<b>.940</b>
<b>Urinary incontinence</b>	<b>.138</b>	<b>2.356</b>	<b>.019*</b>	<b>.105</b>	<b>1.177</b>
Total number of encounters	.045	.837	.403	-.131	.324
Infection	.007	.129	.989	-.416	.474
<b>ADL assistance needed</b>	<b>.160</b>	<b>2.488</b>	<b>.013*</b>	<b>.139</b>	<b>1.194</b>
Pre-admission location (home)	.019	.331	.741	-.481	.675
<b>Braden Scale score</b>	<b>-.142</b>	<b>-2.177</b>	<b>.030*</b>	<b>-.163</b>	<b>-.008</b>
ADL device used	.014	.235	.814	-.437	.556

Adjusted  $R^2 = .266$ ,  $df(14, 263)$ ,  $F = 8.163$ ,  $df(14, 263)$ ,  $p = .000$ , Durbin-Watson = 1.817

<sup>a</sup>. Dependent Variable: Frailty Score

Significant predictor variables highlighted in **Bold**

\*Statistical significance at the .05 level (2-tailed)

\*\*Statistical significance at the .001 level (2-tailed)

Multiple linear regression using the STEPWISE method was then performed with the 14 predictor variables and Frailty Score to determine if a more parsimonious set of predictor variables could be identified. The multiple linear regression model was statistically significant. The STEPWISE multiple linear regression model yielded seven statistically significant predictor variables for the Frailty Score: lower Braden Scale score ADL assistance needed, higher comorbidity count, current tobacco use, female gender, urinary incontinence, and acute pain. The negative coefficient for the Braden Scale score suggests an inverse relationship where a lower Braden Scale score is associated with a higher risk for pressure ulcer development. Collinearity test statistics were acceptable. To

validate the regression model findings and parsimony, multiple linear regressions were repeated for the Frailty Score and the seven predictor variables using the ENTER and STEPWISE method (T. A. Lang & Secic, 2006). The results for the multiple linear regression models were similar and all predictor variables remained statistically significant. Table 18 reports the standardized  $\beta$  coefficients, 95% *CI*, and *p* values for the multiple regression using STEPWISE method.

Table 18

Multiple Regression Coefficients using STEPWISE Method for 14 Significant Predictor Variables and the Frailty Score ( $N = 278$ )

Model <sup>a</sup>	Standardized Coefficients		Sig.	95% <i>CI</i> for $\beta$	
	$\beta$	<i>t</i>		Lower Bound	Upper Bound
Constant		9.775	.000	6.885	10.359
Braden Scale score (lower)	-.201	-3.281	.001**	-.194	-.048
ADL assistance needed	.190	3.345	.001**	.327	1.264
Comorbidity count, higher	.197	3.710	.000**	.040	.132
Tobacco use, current	.166	3.169	.002*	.338	1.449
Gender (female)	.141	2.689	.008*	.150	.971
Urinary incontinence	.146	2.524	.012*	.150	1.211
Acute pain	.109	2.073	.039*	.024	.920
$R^2 = .261$ , $df(1, 270)$ , $F = 15.000$ , $df(14, 263)$ , $p = .000$ , Durbin-Watson test = 1.793					

<sup>a</sup>. Dependent Variable: Frailty Score

\*Statistical significance at the .05 level (2-tailed)

\*\*Statistical significance at the .001 level (2-tailed)

### Comparison of the Multiple Regression Models

Each of the multiple regression models identified seven statistically significant predictors of the Frailty Score. Six predictor variables were common to each of the multiple regression models: lower Braden Scale score, current tobacco use, higher comorbidity, acute pain, ADL assistance needed, and urinary incontinence. Age was the

seventh significant predictor variable in model 1 where multiple linear regression was performed using all 20 candidate predictor variables. In model 2, multiple linear regression using the ENTER and STEPWISE method for 14 predictor variables yielded female gender as the seventh significant predictor variable. In sum, all multiple linear regression models yielded the same six significant predictor variables for the Frailty Score. Age or female gender was significant in some but not all regression models.

### **Research Question 5**

*What is the relationship between level of frailty, or Frailty Score (range, 0 to 14), and hospital length of stay?*

The mean length of stay was 9.92 days (*SD*, 9.58, range, 1-72), the median was 7 days and the mode was 5 days. Simple linear regression was performed to examine if level of frailty or the Frailty Score., the continuous independent variable predicted the continuous dependent variable, hospital length of stay.

Length of stay displayed a non-normal distribution and significant skew and kurtosis. Deletion of outliers and truncation of outliers with substitution of scores at the 50<sup>th</sup> percentile for those cases was performed with little change in distribution parameters. Therefore, log<sup>10</sup> transformation was performed (Field, 2009; Tabachnik & Fidell, 2007). Using the Frailty Score as the predictor variable and the log<sup>10</sup> transformed length of stay variable as the outcome variable, the linear regression model was statistically significant. The standardized  $\beta$  coefficient for the Frailty Score was .053,  $t = 5.319$ ,  $p = .000$ , 95% *CI*, .033 to .072. The adjusted  $R^2 = .090$ ,  $df(1, 276)$ ,  $F = 29.293$ ,  $df(1, 276)$ ,  $p = .000$ . The Durbin-Watson test for correlation among residuals in linear

regression was acceptable (1.983; Field, 2009). Although the regression model was statistically significant, the model explained only 9% of variance in the  $\log^{10}$  transformed length of stay with implications for clinical significance (Field, 2009; T. A. Lang & Secic, 2006).

### **Research Question 6**

*What is the relationship between level of frailty, reflected as the Frailty Score, and 30-day hospital readmission?*

Thirty-day hospital readmission and level of frailty represented as the Frailty Score was examined using logistic regression. Hospital readmission was the outcome binary variable, where “1” indicated 30-day readmission and “0” indicated not readmitted. Thirty-three patients (11.9%) were readmitted within 30 days of discharge. Pearson’s and Spearman’s rho correlation coefficients for the Frailty Score and 30-day readmission were not significant. Logistic regression was conducted with the Frailty Score as the continuous predictor variable and 30-day readmission as the binary outcome variable. Analysis of the logistic regression determined that that the Frailty Score was not a significant predictor of 30-day hospital readmission in this study population. The logistic regression standardized  $\beta$  coefficient for the Frailty Score was .100,  $df(1)$ , 95% *CI*, .913 to 1.337,  $p = .307$ . Observed and predicted values computed as the log-likelihood was used to assess the fit of the model. The -2 log-likelihood for 30-day readmission was 201.497. This finding suggests poor fit and more unexplained observations in the model. The Hosmer and Lemeshow test to evaluate goodness-of-fit of the logistic regression model was not significant, *Chi-square* = 4.121,  $df(5)$ ,  $p = .532$ .

The Wald test statistic was not significant,  $1.043, df(1), p = .307$  (Field, 2009; T. A. Lang & Secic, 2006). The odds ratio *OR* of 1.105 indicated that the odds of 30-day readmission did not change as the Frailty Score increased. Therefore, the (*OR*) was not applicable (Tabachnik & Fidell, 2007).

### Chapter Summary

This descriptive, cross-sectional, retrospective study characterized frailty in acutely ill hospitalized adults 55 years of age and older ( $N = 278$ ). Frailty was characterized by a Frailty Score that was computed by the sum of 14 frailty components defined by 26 indicator variables retrieved from the EMR. Findings from descriptive statistics, tests of association and correlation, and multiple linear regression and logistic regression models were examined to identify significant predictors of level of frailty, or the Frailty Score, and if the Frailty Score predicted longer length of hospital stay, and 30-day hospital readmission.

Higher Frailty Scores were common in the study sample. The mean, mode, and median for the Frailty Score were 9 (*SD*, 1.98, range, 2-13). Fewer than 5% had a Frailty Score of less than five. A slight majority of the sample was female, about one-third were African American, and most were admitted from home. Comorbid illness was prevalent. The mean number of medical diagnoses was 13 and the medication count of prescription and non-prescription medications was 12. Symptom burden was high. A majority of the sample reported fatigue, weakness, ADL dependence, urinary incontinence, vision problems, acute and chronic pain, poor appetite, sleep problems, fever, infection, and abnormal mental status. Over one-third of the sample had unplanned surgery. The mean

Braden Scale score was 18 (*SD*, 3.3, range 9-23), where scores < 18 indicate physiologic vulnerability and high risk for pressure ulcers. About a third of the sample had pressure or vascular ulcers on admission. Nine percent of hospital admissions were related to falls and 27% had a history of falls. Over 89% had abnormal flags for one or more plasma biomarkers that included CRP or hs-CRP, hemoglobin, albumin, and WBC count and two-thirds had abnormal flags for all four. The mean length of stay was about 10 days (*SD*, 9.6, range, 1-72) and 12% were readmitted within 30 days of hospital discharge.

Multiple linear regression models were utilized to identify a parsimonious, statistically significant set of predictor variables. Seven statistically significant predictor variables for the Frailty Score were identified in all models: lower (worse) Braden Scale score, ADL assistance needed, higher comorbidity count, current tobacco use, urinary incontinence, and acute pain. However, only six predictor variables were significant in all models. The seventh significant predictor variable in model 1 was age and in model 2, female gender. Predictor variables significantly associated with frailty in the literature but were not significant predictors in this study were race/ethnicity (Minority) and low body weight or BMI < 18.5 kg/m<sup>2</sup>. In simple linear regression and logistic regression models, the Frailty Score was a significantly predictor of longer length of hospital stay but not 30-day hospital readmission.

## **CHAPTER V**

### **DISCUSSION**

The purpose of this cross-sectional, retrospective, descriptive study was to examine frailty in hospitalized adults 55 years of age and older admitted to general medicine, cardiology, or orthopedic services at a large academic medical center. Limited research suggests that hospitalized older adults are at high risk for frailty and that frail patients experience worse outcomes compared to those who are not frail. However, research about frailty in hospitalized middle-aged and older adults admitted to medicine services was not identified in targeted literature searches. Most research examined frailty in medically-stable community-living older adults and few studies included adults less than 65 years of age. The present study addressed this gap in knowledge by characterizing frailty in hospitalized adults 55 years of age and older. This chapter presents study findings and their implications, limitations, conclusions, and recommendations.

This study was guided by the biological-psychological-social-spiritual (BPSS) model and stress theory. Frailty was defined as a multidimensional, multifactorial syndrome that arises from cumulative dysfunction in BPSS domains that dynamically interact in response to intrinsic and extrinsic stressors over the life course leading to incremental or precipitous decline in physiologic reserve and compensatory function across organ systems and failure to effectively respond to and recover from destabilizing

health events (Abellan van Kan, Rolland, Bergman, et al., 2008; Abellan van Kan et al., 2010; Anpalahan & Gibson, 2007; Bergman et al., 2007; Clegg, 2011; H. J. Cohen, 2000; Engel, 1977, 1981; Ferrucci et al., 2004; Fried et al., 2004, 2005, 2009; Gobbens et al., 2010b; Markle-Reid & Brown, 2003; McEwen, 1993; McEwen & Stellar, 1993; Nowak & Hubbard, 2009; Rockwood et al., 2005; Rockwood, Hogan, & MacKnight, 2000; Santos-Eggimann et al., 2009; T. E. Seeman et al., 1997; Selye, 1955; Walston et al., 2006; Whitson et al., 2007). Fourteen (14) evidence-based frailty components defined by 26 indicator variables characterized frailty. Frailty indicator variables were selected based on close approximation with frailty criteria validated in prior research, alignment with the study conceptual model, and were available in the electronic medical record (EMR). Inclusion of biomarkers associated with inflammation, nutrition, and frailty as frailty components provided physiologic data for laboratory indices with prior significant associations with frailty. The use of readily available data from the EMR was a practical and clinically-relevant first step in characterizing frailty in hospitalized adults. A Frailty Score was computed by summing the 14 frailty components; higher Frailty Scores suggested greater level of frailty.

The study sample consisted of 278 independent hospital encounters for adults 55 years of age and older admitted to the general medicine, cardiology, or orthopedic service of one large academic medical center during a 15-month time period. The mean age was 70 years with good sociodemographic representation. Descriptive data portrayed an acutely ill hospitalized population with high comorbidity and symptom burden, more functional impairment, psychosocial problems, and social support issues, and evidence of

physiologic stress based on high prevalence of abnormal biomarkers. These data supports conceptions of frailty as a multidimensional, multifactorial syndrome and extends understanding of frailty a biologic process associated with aging, disease, disability (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Gobbens et al., 2010a, 2010b; Rønning et al., 2010; Sternberg et al., 2011).

### **Frailty Components and the Frailty Score**

A substantial proportion of the sample had higher Frailty Scores. The Frailty Score mean and range was similar across three age groups with a modest increase with age. These findings suggest that a higher Frailty Score was not unique to the elderly or very old. Study findings identified a high prevalence of frailty components and ADL impairment which was comparable to other studies in hospitalized older adults (Afilalo et al., 2012; R. R. Cohen et al., 2012; Dasgupta et al., 2009; Freiheit et al., 2010; Gharacholou et al., 2012; D. H. Lee et al., 2010; Makary et al., 2010; Sonnenblick, Raveh, Gratch, & Yinnon, 2007). The high prevalence of frailty components and higher Frailty Scores may be associated with unique sample characteristics such as the admitting diagnosis, higher comorbidity, symptom burden, and ADL and mobility impairments, and more complex psychosocial issues requiring increased health and social service needs after discharge. The BPSS factors underlying the frailty components may have been long-standing or temporal to hospitalization.

The most prevalent non-biomarker frailty components were Fatigue, Weakness, Nutrition, Chronic Pain, and Social Support followed by Vision, Cognition, and Depression, each of which have been significantly associated with frailty, inflammation,

stress, and functional impairment in prior research (Bao et al., 2008; Bruce, 2001; K. E. Covinsky et al., 1997, 2010; Kamaruzzaman, Ploubidis, Fletcher, & Ebrahim, 2010; Ní Mhaoláin et al., 2012; Rockwood & Mitnitski, 2007; van Gool et al., 2003). A high proportion had abnormal flags for all four biomarkers. Prior research reports significant associations between low hemoglobin, low albumin, high CRP or hs-CRP, and abnormal WBC counts and frailty, especially in hospital populations (Fukuse et al., 2005; Herrmann et al., 1992; Purser et al., 2006; T. N. Robinson et al., 2009; T. N. Robinson, Wu, et al., 2011; Rønning et al., 2010; Sündermann, Dademasch, Praetorius, et al., 2011; Sündermann, Dademasch, Rastan, et al., 2011).

Study findings were clinically relevant since evidenced-based frailty components defined by sociodemographic, health status, functional, clinical, and laboratory data characterized a high level of frailty in hospitalized adults 55 years of age and older. The literature is replete with evidence for frailty as a geriatric syndrome. The cumulative effects of normal aging processes, morbidity and symptoms, lifestyle behaviors, life stressors and coping strategies, and social support intersect and produce differential risk for frailty and its covert and overt frailty manifestations. In the present study, the greater frequency of higher Frailty Scores across age ranges suggested that the interactive and multiplicative effects of BPSS factors as previously described may have negative repercussions on homeostasis and allostasis of sufficient magnitude to alter physiologic functions and initiate a pathway to frailty. The high prevalence of the frailty components Fatigue, Weakness, Chronic Pain, Depression, and Nutrition, and the four inflammatory biomarkers suggested aberration in physiologic function. These findings might not be

expected in younger hospitalized adults, 55-64 years of age or in older adults who were otherwise healthy and fit prior to acute illness and hospitalization. Study findings provided preliminary descriptive data that challenged the notion of frailty is a syndrome of the aged, the very old, the disabled, persons with multiple morbidity and symptoms, or the terminally ill. Study findings underscore the importance of examining frailty in hospitalized adults 55 years of age and older since higher Frailty Scores were identified across the sample.

### **Frailty Components and Health Status Variables**

There were 20 categorical and quantitative BPSS health status variables in the study. Few frailty components were significantly associated with the demographic variables of age (older), gender (female), and race/ethnicity (Minority) in tests of association. Although causality cannot be assumed, significant associations between health status variables and frailty components showed no consistent patterns with the exception of a few variables that were significantly associated with more frailty components. Not surprisingly, study findings are not in complete agreement with frailty research conducted in community-living adults (Ahmed et al., 2007; Bandeen-Roche et al., 2006; Fernandez-Bolaños et al., 2008; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Hirsch et al., 2006; Santos-Eggimann et al., 2009) and hospitalized adults (Afilalo et al., 2009; Dramé et al., 2008; Hilmer, Perera, et al., 2009; D. H. Lee et al., 2010; Makary et al., 2010). In many studies, demographic variables such as race/ethnicity, gender, and age were significantly associated with frailty components such as comorbidity and symptoms. Unexpectedly, Fatigue was not significantly associated

with any health status variables even though it was the most prevalent non-biomarker frailty component in the study sample and is a significant predictor of frailty in the literature (Bandein-Roche et al., 2006; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Hardy & Studenski, 2010; Xue et al., 2008). The personal experience of the debilitating effects of fatigue among frail elderly has been described (Toye et al., 2006). Given the high prevalence of fatigue in this study sample further analysis is needed. Since the frailty component, Fatigue, was based on self-report and health care provider appraisal, future research in hospitalized adults should include standardized assessment. Fatigue may represent physiologic dysregulation linked to subclinical disease, systemic inflammation, acute illness, comorbidity, psychosocial stress, and increased physiologic effort to maintain homeostasis (Avlund et al., 2006, 2007; Bautmans et al., 2005; Hardy & Studenski, 2008, 2010; Walston et al., 2006).

The frailty component, Dyspnea, was less common; however, dyspnea and fatigue co-occur in many chronic conditions and their combined negative impact on health status and function increases risk for frailty (Ekman et al., 2005; Leidy & Haase, 1996; Walke et al., 2004; K. Woo, 2000). Dyspnea may have been under-reported if it occurred only on exertion. High comorbidity and symptom burden in the sample may have influenced symptom management. For example, dyspnea (and fatigue) may be avoided or minimized by behavioral changes, such as self-imposed reduction in physical activity and mobility and reduced social interaction. The high level of self-reported ADL assistance needed in the study sample may be related to dyspnea and fatigue that was provoked by physical activity needed for self-care and daily function.

Weakness is an undisputedly a significant frailty indicator (Fried, Tangen, et al., 2001; Topinková, 2008; Vanitallie, 2003). However, in this study, Weakness was significantly associated with few variables related to demographics, function, health status, and urinary incontinence. Weakness was among few frailty components significantly associated with age. Weakness was not significantly associated with female gender, where previous research demonstrated significant gender-based differences in strength and muscle mass that may be influential in the higher prevalence of frailty in women compared to men (Fugate Woods et al., 2005; Hubbard & Rockwood, 2011; Santos-Eggiman et al., 2009). Weakness's significant association with age, ADL assistance, and BMI suggests a trilogy of factors that adversely impacts behaviors such as physical activity, which is a critical component in the cycle of frailty.

Notably, the lack of significant associations between Fatigue and any candidate predictor variables leaves a puzzling gap in understanding frailty since weakness and fatigue interact in reciprocal ways that lead to progressive reduction in the frequency, duration, and intensity of physical activity with deleterious consequences including frailty (Landi, Abbatecola, et al., 2010; Peterson et al., 2009; Weiss, Hoenig, Varadhan, Simonsick, & Fried, 2010; Xue et al., 2008; Yang & Lee, 2010).

Nutrition was significantly associated with two variables, demographic (admission from home) and behavior (tobacco use). In this study, unplanned weight loss and poor appetite was documented in a considerable proportion of the sample. In prior research, nutritional deficits, malnutrition, unplanned weight loss, poor appetite, and low BMI were significantly associated with frailty (Bartali et al., 2006; Fried, Tangen, et al.,

2001; Hogan et al., 2003; Lally & Crome, 2007; Levers et al., 2006; Markle-Reid & Browne, 2003; Rodríguez-Mañas et al., 2012; J. Woo, Leung, & Morley, 2012). Poor appetite and nutrient intake and unintentional weight loss in persons who are overweight is associated with frailty criteria such as weakness, fatigue, lower physical activity, sarcopenia, and with frailty (Bales & Ritchie, 2002; Villareal et al., 2006; Jarosz & Bellar, 2009; Kinney, 2004). In this study, over half of the sample was overweight or obese. Obesity may be an important predictor of frailty since adipose tissue is a biologically active source of proinflammatory cytokines such as CRP that contributes to chronic systemic inflammation and a catabolic state that leads to muscle wasting and sarcopenia, key frailty indicators (Blaum et al., 2005; Cooper et al., 2012; Hubbard & Woodhouse, 2010; Jarosz & Bellar, 2009; Visser, 2011). Catabolic processes can be exacerbated since obesity has been linked to high caloric but poor nutrient intake (Kaiser, Bandinelli, & Lunenfeld, 2009; Kaiser et al., 2010). In the present study, weight loss and poor appetite may be related to acute illness or chronic disease exacerbation, and may not an indicator of a progressive and irreversible pathway of decline that leads to malnutrition and frailty (Kaiser et al., 2010).

Almost half of the sample had Braden Scale scores < 18, which suggests global physiologic vulnerability, nutritional and mobility problems, and higher risk for pressure ulcers. The sample was also characterized by ADL dependence and abnormal biomarkers associated with malnutrition, but none of the biomarkers were significantly associated with Nutrition. However, the high prevalence of abnormal flags for Albumin (low) and Hemoglobin (low) suggests malnutrition may have been a persistent problem.

In this study, Chronic Pain was not significantly correlated with comorbidity or polypharmacy despite evidence that adults often experience multiple sources of pain that arises from multiple conditions and require multiple types of analgesics. There is limited research on chronic pain and frailty. In one study, frail men with high comorbidity were significantly more likely to report pain compared to healthy men (Blythe et al., 2008). Chronic pain adversely impacts biologic processes, symptoms, function, and behaviors that set the stage for frailty across the life span (Whitson et al., 2009). Considering that hospitalized adults may experience different sources and types of pain, it is essential that pain assessment and intervention is comprehensive as this is more likely to promote rapid recovery, improve function, and prevent frailty (Rastogi & Meek, 2013). Chronic Pain was the only frailty component significantly associated with physician documentation of failure-to-thrive or frail on admission. This finding underscores the importance of interdisciplinary communication and collaboration to optimize pain management.

As shown in previous studies, Cognition in this study was significantly associated with age, function, symptoms, and health status. Cognition indicator variables, cognitive impairment and delirium, are each significantly and independently associated with frailty and worse outcomes (Ávila-Funes et al., 2009; Boyle, Buchman, Wilson, Bienias, & Bennett, 2007; Buchman, Boyle, Wilson, Tang, & Bennett, 2007; Inouye et al., 2007; Mitnitski et al., 2011; Panza et al., 2011; Rothman et al., 2008; Song, Mitnitski, & Rockwood, 2010, 2011). Cognitive impairment of any type is important in hospitalized adults since it is associated with iatrogenic events, poor prognosis, longer length of stay, readmission, and mortality (Eeles et al., 2012; Inouye & Charpentier, 1996; Khan et al.,

2012; Quinlan et al., 2011). Delirium warrants attention since it may be a cognitive manifestation of frailty due to compromised multisystem function and compensatory reserve that precipitates or accelerates progression of frailty (Inouye et al., 1999, 2007; Quinlan et al., 2011).

In accordance with prior research, Depression was significantly associated with demographics (race/ethnicity [Minority]) and health status (Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; (Bookwala & Lawson, 2011; Lenze et al., 2005; Mezuk et al., 2011; Ní Mhaoláinet al., 2012; van Gool et al., 2003; Whitson et al., 2007). Depression occurs at higher rates in African-Americans who are frail (Hirsch et al., 2006; Szanton et al., 2005). Significantly higher rates of depression and CRP levels have been documented in African American compared to White community-living younger and older adults, independent of demographic and health status risk factors, and behaviors (Deverts et al., 2010). In the present study, high CRP or hs-CRP was not significantly associated with race/ethnicity (Minority).

Similar to previous research, Falls were significantly associated with age, physical function, symptoms (urinary incontinence), and behaviors (current tobacco use), which are each significantly associated with frailty (Ensrud et al., 2007, 2008, 2009; Inouye et al., 2007). Prior research substantiates significant associations between falls and frailty, injury, functional decline, dependence, and mortality (Anpalahan, & Gibson, 2007; Ensrud et al., 2007, 2008, 2009; Fried, Tangen, et al., 2001; Fugate Woods et al., 2005; Hilmer, Perera, et al., 2009; Runge & Hunter, 2006; Pol et al., 2011; Nelson, Dufraux, Cook, 2007; T. N. Robinson, Wallace, et al., 2011; Speciale et al., 2004). In this study,

current tobacco use was documented in a small percentage of the sample, however, tobacco use warrants attention since it is associated with poor physical function, chronic inflammation, and frailty (Hubbard et al., 2009; Rapuri et al., 2007). In one study, heavy smokers were the most frail, light smokers were intermediate frail, and those who never smoked were the fittest (Hubbard et al., 2009). In this study, only data on current tobacco use was available. Data on lifelong smoking patterns may yield different findings.

Vision problems were significantly associated with demographic, clinical, and health status variables. The findings of this study are in agreement with other studies where vision impairment is associated with frailty (Brody et al., 2001; B. K. Keller, Morton, Thomas, & Potter, 1999; Klein, Klein, et al., 2003; Whitson, Ansah, et al., 2010). In the present study, Vision was significantly associated with comorbidity but not ADL impairment. Vision impairment affects risk for frailty through adverse effects on physical and cognitive function, mobility, fall risk, social interaction, and mood (Bookwala & Lawson, 2011; Klein, Klein, et al., 2003). Prior research has found significant relationships between poor vision and cognitive impairment, mobility impairment, and disability where the estimated odds ratio associated with combined poor vision and cognitive impairment was greater than the estimated odds ratio associated with poor vision or cognitive impairment alone (Whitson et al., 2007). Frailty is considered as a pre-disability condition in most cases, thus attention to vision and cognition is warranted (Abellan van Kan, Rolland, Bergman, et al., 2008).

In this study, Social Support concerns were significantly associated with demographics, function, symptoms, health status, behaviors, and spirituality. Social

Support significantly correlated with the most health status variables, suggesting that factors other than biologic processes may be contributory to health status and frailty (Andrew et al., 2008; T. E. Seeman, 1997; T. E. Seeman et al., 2003). Previous reports cite similar findings where psychosocial factors, social determinants, inadequate social networks, and lack of needed social support resources adversely impact health status, function, and risk for frailty (Bilotta et al., 2010; Loucks, Berkman, et al., 2006; Loucks, Sullivan, et al., 2006; Newsom & Schulz, 1996; Rockwood & Bergman, 2012). Social vulnerability and frailty has been studied by examining relationships between biologic markers and measures of cumulative BPSS stress and the impact on individual and across physiologic systems. Higher numbers of abnormal biomarkers (allostatic load) has been associated with physiologic dysregulation and frailty (Gruenewald et al., 2009; Rockwood & Bergman, 2012; T. E. Seeman et al., 1997; Szanton et al., 2009). In the present study, four biologic markers provided physiologic evidence of potential dysregulated systemic processes. Despite the high prevalence of abnormal biomarkers, there were no patterns of association between biomarkers and demographic and BPSS health status variables.

Abnormal flag for WBC count (abnormal) was significantly associated with the most variables including demographic, health status, and function. Research indicates that abnormal WBC count is a significant predictor of frailty in community-living women (Leng et al., 2005; Leng, Hung, et al., 2009; Leng, Xue, et al., 2009). In the present study, the abnormal flag for WBC count may be a temporal finding related to admission diagnoses of infection, pressure orvascular ulcer, and urinary incontinence. WBC count

was the only biomarker significantly associated with age. In a study of younger and older adults ( $n = 196$ , 20–35 years;  $n = 314$ , 70–85 years, Denmark) the number of leukocytes, lymphocytes and neutrophils was associated with fatigue in both age groups (Avlund et al., 2012). Among older adults, the relationship between fatigue and leukocytes, lymphocytes and neutrophils was not significant when adjusting for physical activity and disability and in the younger group, the relationship between neutrophils and fatigue was not significant when adjusting for depression. There may be a potential role of leukocytes, neutrophils and lymphocytes in development of fatigue. In the present study, tests of association between Fatigue and WBC count were not statistically significant.

Abnormal flag for CRP or hs-CRP was significantly associated with health status, chronic disease, and symptoms. In community-living older men hs-CRP levels were significantly higher in frail than non-frail men (Almeida, Norman, van Bockxmeer, Hankey, & Flicker, 2012). In hospitalized adults, CRP is used to assess acute infection, treatment response, and surgical recovery. However, relationships between CRP or hs-CRP and frailty have not been studied in hospitalized adults.

Abnormal flag for Albumin level was also highly prevalent in this study and was significantly associated with function and health status. Research in hospitalized adults identifies low albumin level is a significant predictor of morbidity and has been suggested as a composite marker for chronic disease, poor nutritional status, functional impairment, and frailty. In this study, findings are in agreement where abnormal flag for Albumin (low) was significantly associated with poor ADL function and low Braden Scale score, a composite indicator of multisystem dysfunction (Arques et al., 2008; Corti

et al., 1994; K. E. Covinsky et al., 1999; Herrmann et al., 1992). A particularly relevant finding of this study is the high prevalence of low albumin and high CRP or hs-CRP levels. Research indicates that the combination of low albumin levels and high levels of CRP are significant predictors of frailty, evidence that is germane to the present study and warrants further analysis (Nelson et al., 2000; Visser et al., 2005; Wu, Shiesh, Kuo, & Lin, 2009). Hemoglobin abnormal flag (low) was significantly associated only with medication count. Low hemoglobin level and anemia are associated with decreased muscle strength and physical performance in older adults but in this study, there were no significant associations with any of the variables for demographics, symptoms, health status, and function (Izaks et al., 1999; Penninx et al., 2004). This finding is unexpected since tissue and organ oxygenation and perfusion are dependent on the iron-binding capacity of hemoglobin. Significant associations with demographic, function, and health status variables would be biologically relevant.

In future analyses, using the actual plasma value rather than abnormal flag may yield different findings. There may be thresholds for each biomarker that significantly differentiate level of risk and increased vulnerability for frailty. Research indicates that even modest deviations from the reference range for multiple biomarkers (which suggests failure of homeostasis and allostasis resulting in increased allostatic load) is more predictive of multisystem dysregulation that is associated with frailty than any one highly abnormal biomarker (Gruenewald et al., 2009; McCaffery, Marsland, Strohacker, Muldoon, & Manuck, 2012). There is no known research on which biomarkers are most

appropriate, clinically relevant, feasible, cost-effective, and the laboratory value cutpoints for frailty risk stratification and outcome prediction in hospitalized adults.

### **Demographic, Biological, Psychological, Social-Spiritual Variables and Frailty Score**

Relationships between demographic, biological, psychological, social-spiritual variables and the Frailty Score were analyzed in multiple linear regression models. Seven predictor variables were yielded in three regression models: one regression model for the 20 candidate predictor variables and two models for the 14 candidate predictor variables. In each regression model, six predictor variables were identical: lower Braden Scale Score, higher comorbidity, acute pain, urinary incontinence, current tobacco use, and ADL assistance needed. The seventh predictor variable in the first multiple regression model with 20 predictor variables was age and in the second model where multiple regression was performed using the ENTER and STEPWISE method with 14 candidate predictor variables, female gender. None of the demographic variables (age, race/ethnicity [Minority], female gender) were significant predictors in all regression models. Race/ethnicity (Minority, mostly Black) was not a significant predictor in any of the regression models in contrast to prior research where higher level of frailty is significantly associated with African American race (Hirsch et al., 2006; Xue, 2011). In the Women's Health and Aging Study, African American race was significantly associated with frailty but not when adjusted for income and education; older White women had the same odds for frailty as African American women based on lower socioeconomic status (Szanton, Seplaki, et al., 2010).

Age is an important frailty predictor since advancing age is associated with multi-organ system changes related to normal aging and disease processes, increased prevalence of disease and symptoms, functional limitations, and detrimental lifestyle changes (Izaks & Westendorp, 2003; Fried et al., 2001; Mitnitski, Graham, Mogilner, & Rockwood, 2002; Rockwood, Song, & Mitnitski, 2011). In this study, age and Frailty Score means and ranges were similar across age tertiles. Thus, some hospitalized adults in the 55 to 64 year old age group had more frailty components than might be expected for their age, while some in the 75 years of age and older had fewer frailty components than might be expected for their age. Although Frailty Scores increased modestly with age, study findings affirm that older age is not synonymous with frailty in part due to heterogeneity in the aging population. Since aging changes advance at different rates in organ systems and experience and cope with age-related changes and disease conditions in different ways explains the loose correlation between biologic and chronologic age (Bortz, 1993, 2002; 2010; Mitnitski et al., 2002). While age and multiple morbidity are often used to estimate risk for adverse outcomes related to medical or surgical interventions, findings from the present study suggest that frailty assessment may provide additional information about overt or covert biopsychosocial vulnerabilities and risk for poor outcomes in hospitalized adults (D. H. Lee et al., 2010).

Race/ethnicity (Minority) was not a significant predictor of the Frailty Score which contrasts with research that identifies higher prevalence and severity of frailty in African Americans, especially African American women compared to white men and women (Fugate Woods et al., 2005; Hirsch et al., 2006; Szanton et al., 2009). Other

factors not measured in this study may be influential such as education attainment, socioeconomic status and financial security, social position, living environment, occupation, access to health care, health care quality, biopsychosocial factors, life stressors, level of cumulative stress, sociocultural factors (racism, sexism, ageism, classism), and social determinants.

Comorbidity and medication count was high in this study sample. Several frailty definitions use a count of medical conditions (Farhat et al., 2011; Kulminski, Ukraintseva, Culminskaya, Arbeev, Land, Akushevich, & Yashin, 2008; Rockwood et al., 2005). Medical condition counts provide an estimation of disease burden but clinical and symptom manifestations can vary thus underestimating the clinical significance and relevance with respect to BPSS function and stress.

The Braden Scale score was a significant predictor of the Frailty Score in the three regression models. Almost half of the study sample had low Braden Scale scores indicating multisystem vulnerability. The Braden Scale score significantly correlated with eight of 14 frailty components, including three biomarkers, health status, age, and hospital length of stay. In a study of hospitalized older adults who underwent abdominal surgery, where frailty was defined by the deficit accumulation framework and 39 predictor variables, the Braden Scale score was the only significant predictor of post-operative complications (Cohen et al., 2012). Because the Braden Scale is a composite score for six subscales that when summed, estimate aggregated risk associated with multisystem impairments, it captures a more global depiction of biologic vulnerability that is more than a composite of loosely related or unrelated deficits.

Research indicates that frailty is significantly associated with longer length of stay. In the present study, the Frailty Score was significantly associated with longer length of stay (Afilalo et al., 2010; D. H. Lee et al., 2010; Ostir, Berges, Kuo, Goodwin, Ottenbacher, & Guralnik, 2012; Sunderman et al., 2011; Winograd et al., 1991). According to the U.S. Census Bureau, mean length of stay for hospitalized patients 65 years and older was 5.7 days compared to four days in patients younger than 65 years (U.S. Census Bureau, 2003). In a study of older adults admitted for elective surgery, preoperative frailty defined by the Fried Frailty Index was significantly associated with longer length of stay (intermediate frailty: incidence rate ratio (*IRR*) = 1.49, 95% *CI*, 1.24-1.80; frail: *IRR* = 1.69, 95% *CI*, 1.28-2.23) (Makary et al., 2010). Frailty assessment improved the predictive power ( $p < 0.01$ ) of other risk assessment indices. In cardiology inpatients, two frailty indices and individual performance measures were significant predictors of longer length of stay (Purser et al., 2005). In a study of hospitalized older adults, significant predictors of longer length of stay were walking difficulties, fall risk, malnutrition risk, and cognitive impairment (P. O. Lang et al., 2006).

The Frailty Score was not significantly associated with 30-day readmission in this study. Substantive research demonstrates significant associations between frailty and hospital readmission (Andrew et al., 2008; Fugate Woods et al., 2005; J. E. Carlson et al., 1998; Goldstein, Dominguez, & Vallone, 1991; Landi et al., 2004; Marcantonio et al., 1988; Marcantonio et al., 1999; Williams et al., 1988; Winograd et al., 1991; Woo et al., 2005). In the present study, the high prevalence of symptoms in the Frailty Score was notable (e.g., fatigue, weakness, poor appetite, dyspnea, acute pain, chronic pain, urinary

incontinence, fever, depressive symptoms, poor vision). Co-occurring symptoms and their deleterious effects are associated with higher hospitalization rates (Gill et al., 1999; Fried et al., 2009; Jarrett et al., 1995; Whitson et al., 2009). Although the Frailty Score did not predict 30-day readmission in this study, this finding should not overshadow the evidence that 37 percent had two or more hospitalizations and four percent had four or more hospitalizations during the study time period. In addition, since data collection did not track admissions to other hospitals, it is possible that the 30-day readmission is underestimated. Characteristics of patients who were and were not readmitted within 30 days of discharge were not analyzed in this study.

### **Implications**

Frailty was characterized by a multidimensional Frailty Score that included 14 evidence-based frailty components defined by 26 indicators including four biomarkers associated with inflammation, malnutrition, and frailty. The sample is atypical since all four biomarkers are not commonly ordered in hospitalized adults. The Frailty Score significantly predicted longer hospital length of stay but not 30-day readmission in hospitalized adults 55 years of age and older admitted to the general medicine, cardiology, or orthopedic service in one academic medical center.

The Frailty Score mean and range was similar across three age groups. Although the majority of frailty research characterizes frailty as a syndrome of the aged and concentrates research in community-living, medically stable older adults, a few studies have examined frailty in community-living middle-aged adults (Chen, Wu, Chen, & Lue, 2010; Santos-Eggimann et al., 2009) and hospitalized adults age 60 years of age and

older (Fukuse et al., 2005). Identifying frailty in hospitalized adults 55 years and older is important because there is potential for greater benefit from prevention and intervention strategies in this group compared to the very aged, where frailty may be more advanced and compounded by physiologic aging changes, comorbidity, and disability.

Interventions targeted to midlife adults and older adults who have lower Frailty Scores may be more likely to benefit from interventions to prevent, delay, or halt progression of frailty. In the very aged, when frailty is more advanced and compounded by aging changes and chronic disease, the magnitude of benefit from interventions may be limited. However, a nihilistic approach to frailty prevention and intervention in the elderly or very old is both unwarranted and unethical since research has found that interventions focused on physical activity, mobility, and nutrition for example can yield significant benefit. Sensitive attention to patient and family preferences is important as the RN is often in a position to encourage and facilitate active engagement in living life fully and functioning at a level that is in accordance with patient and family wishes. Symptom management would be essential to make active engagement feasible. It is also appropriate, however, to consider compassionate care interventions for frailty at advanced stages when there are physiologic and BPSS indicators of transition to the end-of-life or active dying phase.

In this study, high comorbidity was common and was a significant predictor of the Frailty Score. Most frailty research finds significant associations between higher comorbidity and frailty (Bandeem-Roche et al., 2006; Fried et al., 2001; Fugate Woods et al., 2005; Weiss, 2011). However, studies that do not find significant associations between comorbidity and frailty lend support to the concept that frailty is a distinct

clinical syndrome (Bandeem-Roche et al., 2006; Fried et al., 2004). Alternatively, a high medication count was almost universal but was not a significant predictor of the Frailty Score. The Braden Scale score was a significant predictor of the Frailty Score. Few frailty studies have examined pressure ulcer risk assessment instruments such as the Braden Scale as a predictor or correlate of frailty in hospitalized adults. In a study of hospitalized older adults following abdominal surgery the Braden Scale score was the only significant predictor of post-operative complications, longer length of stay, and discharge to an institution rather than home (R. R. Cohen et al., 2012). In a study comparing four uniquely different frailty instruments in hospitalized older adults admitted to geriatric units (N = 2,033,  $\geq 65$  years, Italy) and mortality prediction (Pilotto et al., 2012). The four instruments were the FI-SOF (modified version of the Fried Frailty Scale used in the Study of Osteoporotic Fractures), the FI-CD (Frailty Index based on the cumulative deficit framework), the FI-CGA (Frailty Index based on comprehensive geriatric assessment), and the MPI (Multidimensional Prognostic Index). The MPI includes eight domains (function, cognition, nutrition, comorbidity, medications, co-habitation status, and the Exton Smith Scale, a pressure ulcer risk assessment instrument). All-cause mortality rates were 8.6% after one-month and 24.9% after one-year follow-up. All four frailty instruments were significantly associated with one-month and one-year all-cause mortality however the MPI demonstrated significantly higher discriminatory power for prediction of one-year mortality compared to the three other instruments for patients without ADL or IADL functional limitations (or both) or cognitive impairment and greater prognostic accuracy in patients with malnutrition, comorbidity ( $>3$  medications),

and polypharmacy (>7 medications). Inclusion of pressure ulcer risk assessment in frailty assessment requires further investigation.

In the present study, there was a high prevalence of frailty components that represented symptoms. Symptom burden can adversely affect BPSS function, increase stress, and worsen inflammatory processes that increase risk for frailty or hastens its progression and severity. Symptom burden and symptom expression may be important in frailty since symptom manifestations represent a more global indication of physiologic capacity for homeostasis. In a study examining chronic disease, symptoms, and function in older adults, symptoms were more relevant indicators of function and disability than medical diagnoses, findings that are pertinent to frailty (Whitson et al., 2009). In the care of frail adults, symptoms are crucial targets for intervention (Morley, 2010; Newman et al., 2010; O'Connell, Hawkins, Baker, & Ostaszkievicz, 2011; Schultz-Larsen & Avlund, 2006; Shega et al., 2011). The high prevalence of distressing symptoms in hospitalized adults requires a multifaceted approach to symptom assessment, using standardized tools to evaluate symptom quality and severity, and a range of interventions that may alleviate individual symptoms as well as symptom clusters (Chen et al., 2011).

Fatigue definitions and measurement vary across studies and may include questions about tiredness, energy level, difficulty getting going, trouble sleeping, poor concentration, weakness, and ADL function (Avlund et al., 2006; Bandeen-Roche et al., 2006; Fried et al., 2001; Fugate-Woods et al., 2005; Hardy & Studenski, 2010; Xue et al., 2008). Fatigue impacts risk for or progression of frailty due to greater physiologic effort to maintain homeostasis in the context of subclinical disease, comorbidity, symptoms,

and biopsychosocial stressors (Avlund, Damsgaard, Sakari-Rantala, Laukkanen, & Schroll, 2002; Bautmans et al., 2005; Hardy & Studenski, 2008, 2010; Schultz-Larsen & Avlund, 2006; Walston et al., 2006; Woo, 2000).

Chronic pain is important in frailty since it reduces the capacity to respond to biopsychosocial stressors. In the present study, chronic pain was reported by over a quarter of the sample. There can be multiple sources of chronic pain, which was not addressed in this study. In the hospitalized setting, acute pain may command greater attention than chronic pain due to common conditions such as osteoarthritis. In acutely ill, instable patients, chronic pain may be under-treated. Attention to alleviation of chronic and acute pain may facilitate mobility and recovery and reduce risk for depression, delirium, poor nutritional intake, incontinence, incident frailty, and lessen severity or progression of frailty (Davis, Robinson, Le, & Xie, 2011; Jarrett et al., 1995; Pine et al., 2000).

Depression is significantly associated with frailty. Depression is common in adults and often overlooked. In a study of community-living adults 60 years of age and older, those who were classified as pre-frail or frail had significantly higher depression scores compared to nonfrail adults (Ní Mhaoláin et al., 2012). In a systematic review of depression and frailty, a number of studies supported a bidirectional relationship between frailty and depression (Mezuk et al., 2011). Assessment of depression would facilitate early diagnosis and treatment and reduce risk for or worsening of frailty (Inouye et al., 2007; Ní Mhaoláin et al., 2012).

In hospital settings, risk assessments are commonly performed for falls, pain, and pressure ulcers as standard nursing practice. As a syndrome, frailty represents a more unstable, vulnerable state that may be a final common pathway for syndromes such as falls, delirium, pain, malnutrition, urinary incontinence, functional decline, and pressure ulcers (Anpalahan & Gibson, 2007; Inouye et al., 2007). Comprehensive frailty assessment that incorporates risk factors for geriatric syndromes could improve precision in identifying high risk hospitalized adults. Nursing leadership would be critical in coordinating communication, and collaboration among interdisciplinary team members to facilitate optimal care for hospitalized adults who are at risk for frailty or who are frail.

### **Strengths**

The present study addressed a gap in knowledge by examining frailty defined by 14 frailty components in a younger acutely ill hospitalized adult population 55 years of age and older. Study findings challenge the notion that frailty is unique to the aged or very old since higher Frailty Scores were documented across age tertiles. Rather than frailty being defined as a geriatric syndrome, it is better understood as a condition associated with complex, nonlinear physiologic interactions across multiple body systems that are influenced by intrinsic and extrinsic stressors that incite inflammation and other systemic responses (Fried et al., 2009). The intersection of multifactorial BPSS stressors, vulnerabilities, and pathologies exert cumulative adverse effects on health status and sets the stage for frailty.

Frailty research in hospitalized adults has focused more on pre-operative surgical risk in the elderly, usually among those 70 years of age and older. Demographic data

portray an aging population that is living longer with increasing numbers who elect to undergo surgical and other invasive procedures to not only potentially extend the lifespan but most importantly, to improve quality of life. There is evidence that pre-operative risk assessment tools often fail to identify those at high risk for poor post-operative outcomes. Frailty measures and instruments have been utilized as an adjunct in preoperative risk assessment to improve detection of patients more likely to experience post-operative complications, mortality, and other adverse outcomes (Afilalo et al., 2010, 2012; R. R. Cohen et al., 2012; Makary et al., 2010). The present study examined frailty in a naturalistic sample of medical admissions with few exclusion criteria. This is an understudied population. The use of a systematic approach to construct a study sample using a data query tool facilitated selection of variables associated with frailty and construction of a dataset with sufficient power for statistical analyses. The study sample was medically complex, had higher mean Frailty Scores, more comorbidity and symptoms and longer length of stay. Frailty characterization provided a different lens to view population acuity, risk factors, BPSS needs, domains of assessment and priorities in clinical care and discharge planning.

### **Limitations**

The study had several limitations. The study design was cross-sectional, descriptive, and retrospective. EMR data extraction focused on health status on admission thus frailty was characterized at a static moment in time. The natural history of frailty and transitions in level of frailty before, during, and after hospitalization could not be examined. The study population included medical admissions at a large academic

medical center. Some admissions were referred for specialist treatment and diagnostic procedures not available at other hospitals. The study sample may represent a more acutely ill, medically complex group compared to community or regional hospitals. Some patients had unplanned surgery or invasive procedures. Data on surgery, procedures, and intensive care unit transfers was not collected.

Secondary analysis of medical records is associated with the risk for incomplete, inaccurate, or missing data. Variables selected to represent the demographic, biologic, psychologic, social-spiritual domains and the 14 frailty components were limited to observational data available in the EMR. Frailty criteria cited in the literature with demonstrated validity such as standardized assessment instruments for ADL and IADL function, mobility, strength, cognitive function, depression, symptoms, and social networks and support, for example, were not available. Data recorded on the nursing and physician admission assessment relies heavily on patient self-report or information provided by a proxy. Pol and colleagues (2011) compared the validity of self- and proxy-report of ADL and IADL function and found moderate to good agreement between patients and proxies (70%–90%,  $p < .001$ ). Cognitive impairment and delirium were significantly associated with greater disagreement. Comparison of patient and proxy ratings with clinician-observed performance was not conducted. In the present study, degree of mobility and functional impairments were not quantified and standardized instruments were not used. EMR documentation was conducted according to hospital policy and professional standards. Provider expertise, time constraints, and the patient or patient proxy's ability to provide accurate information were potential threats to reliability

and validity of information recorded in the EMR. To ensure data integrity, multiple sources in the EMR were reviewed to cross-validate information. Data verification of data collection forms and analytic database was performed for the full sample.

Inclusion criteria included laboratory data for four plasma biomarkers not routinely ordered for all hospital admissions. Medical factors that warranted ordering all four biomarkers during one hospital encounter may significantly differentiate this group from other hospitalized adults. The study sample may be unique since descriptive data portrayed high comorbidity, polypharmacy, ADL impairment, and symptom burden, and social support concerns in this group. Thus, the Frailty Score may over-estimate level of frailty in this hospitalized adult population. External validity is of concern and generalizability of study findings is limited.

The relative contribution of each biomarker individually and in combinations was not examined in this study and requires further analysis. The addition of other hematologic, urine, and salivary biomarkers (e.g., fasting blood glucose, glycosylated hemoglobin, creatinine, high density lipoprotein, blood urea nitrogen, creatinine clearance, cortisol, others) should also be considered as these are associated with inflammation and multi-organ system function. Other biomarkers that are readily available or may be prospectively obtained such as systolic and diastolic blood pressure, BMI, waist circumference, heart rate variability, ejection fraction, and others, may improve frailty characterization.

Length of stay may have been influenced by patient and family preferences for care that changed during the hospital course. About a third of admissions involved

unplanned surgery. Failed medical treatment of complex problems that resulted in surgical intervention may have contributed to longer length of stay. Subgroup analysis of unplanned surgery was not conducted in this study. Length of stay may have been influenced by cascade iatrogenesis, or the serial development of multiple potentially preventable medical problems that arise from a minor event often unrelated to the reason for admission and snowball as other problems develop resulting in continued need for acute care (Creditor, 1993; Mitty, 2010; Thornlow et al., 2009).

### **Conclusion**

In this hospitalized sample of 278 adults age 55 years and older, high comorbidity and symptom burden, polypharmacy, ADL impairment, high prevalence of infection and pressure or vascular ulcers, lower Braden Scale scores, and frequent unplanned surgery suggested a high level of medical acuity, complexity, dependence, and greater psychosocial needs. The mean Frailty Score was high and younger age was not protective lending support to the notion that frailty was not unique to the aged, very old, or terminally ill. The most prevalent non-biomarker frailty components were Fatigue, Weakness, and Nutrition. A majority of the sample had three or four abnormal biomarkers suggesting compromised physiologic function, homeostasis, and compensatory reserve. Almost half of the sample had lower Braden Scale scores suggesting biologic vulnerability. The Braden Scale was significantly associated with the most frailty components and demographic and BPSS variables. In different multiple regression models, eight predictor variables were statistically significant predictors of the Frailty Score. Six predictor variables were common to all three models: Braden Scale

score, ADL assistance, comorbidity, tobacco use, urinary incontinence, and acute pain. In two regression models, female gender was significant, whereas age was significant in one regression model. In linear regression and logistic regression models, the Frailty Score significantly predicted longer hospital length of stay but not 30-day hospital readmission.

In sum, external validity and generalizability of study findings are limited by the unique features of the sample and setting, thus study findings should be interpreted in consideration of these limitations.

### **Recommendations for Education, Practice, and Research**

The following recommendations are proposed for nursing education, practice, research, and public policy.

#### **Education**

Research over 30 years has substantiated the importance of frailty with significant implications for nursing practice across clinical settings and in the community. Nursing education must keep pace with the growing body of literature on frailty. A nursing diagnosis for frailty has not been defined or published (NANDA International, 2011). In order for nursing education to advance in addressing frailty in the curriculum to prepare learners for future clinical practice, a conceptual and operational definition for a nursing diagnosis for frailty needs to be developed, validated, and published. This would increase awareness of this syndrome and provide guidance to nursing faculty and students, as well as clinicians, and researchers. Differentiating failure-to-thrive from frailty is important, as previously discussed, since clinical decision-making would be potentially biased since these terms are often used synonymously. Assuming that frailty is an end-stage condition

with no hope for amelioration can lead to passivity and therapeutic nihilism despite evidence that frailty may be improved or reversed. Conversely, differentiating these two conditions would guide decision-making about when to initiate palliative care and symptom management (instead of continuing exhaustive diagnostic testing or treatments associated with adverse side effects) and discussions about end-of-life care are most appropriate (Raudonis & Daniel, 2010). Patient preferences for care must also be considered since research suggests that hospitalized frail elderly value good communication and information about health status and if able, participation in decision making about care (Ek Dahl et al., 2010). This approach is critical in nursing education where the concept of caring is central to person-centered care. Nursing care and caring of frail adults requires caring skills that balance protection and independence, help find meaning in life, preserves quality of life, and advocates for the preferences and needs of this vulnerable population (Erlen, 2007; Heath & Phair, 2009).

Innovative teaching strategies about frailty are needed for classroom and clinical instruction across the nursing curriculum. Classroom instruction that incorporates selected readings, resources, and active learning strategies (case studies, high and low fidelity simulations, role play, interviews with older adults, individual and group assignments focused on different frailty trajectories in relation to different nursing practices and models of care). Preventing hazards of hospitalization and functional decline is a high priority nursing concern (Anpalahan & Gibson, 2007; Boltz et al., 2012; Brown, Williams, Woodby, Davis, & Allman, 2007; K. E. Covinsky et al., 2003; Creditor, 1993). Content on the impact of public policy and health care financing on

health disparities and vulnerable populations (local, regional, national, global issues) would elucidate factors that unfairly predisposes some persons to frailty (Albert, Im, & Raveis, 2002; Geronimus, 2001; Geronimus et al., 2006, 2007; James et al., 1992; Kuh, 2007; Kuchel, 2009; Laditka & Laditka, 2002; Mullings, 2005; Szanton et al., 2005; Whitson et al., 2011). Frailty is an ideal paradigm for the unfolding case study that could examine a single hospitalization experience or take a more a life-course approach. These and other learning experiences would facilitate analysis and application of complex concepts of multidimensional frailty, physiologic loss of complexity, and importantly, nursing implications for clinical leadership in direct care and in system change.

Clinical learning experiences applying the nursing process would enhance critical thinking and clinical reasoning skills in the comprehensive multidimensional assessment of frailty. Active collaboration with the interdisciplinary team to communicate diverse clinical information to develop, in collaboration with the patient, family and significant others, an individualized plan of care capitalizes on disciplinary expertise and facilitates person-centered care and optimal health status outcomes. Curricular content on how to work with interdisciplinary teams and to assert clinical leadership at the bedside is needed since much of nursing education focuses on direct care of patients (Benner, Sutphen, Leonard, & Day, 2010; Byrum, 2001; Grossman & Valiga, 2013; A. Robinson & Street, 2004; Dyer et al., 2003). Nurses in direct care positions must be prepared to initiate and facilitate effective interdisciplinary communication, collaboration, and care coordination (Byrum, 2010; Walker, Hogstel, & Curry, 2007).

In hospital and home health care settings where federal guidelines have enacted pay-for-performance models with financial penalties for 30-day hospital readmission and long length of stay, frailty screening and comprehensive interdisciplinary assessment and care coordination will aid in optimizing quality of care and outcomes. Assessment and prevention/intervention protocols are integrated in nursing practice in many hospital settings for geriatric syndromes such as falls, mobility, pressure ulcers, pain, urinary incontinence, and delirium. Education is needed about how nurses can use data generated from comprehensive frailty assessment is assimilated into algorithms that identify frailty risk level and guide primary and secondary prevention and targeted intervention. Increased attention in nursing education to geriatrics, geriatric syndromes and frailty is crucial. Attention to preventable untoward events is of paramount importance as federal guidelines and other regulatory bodies emphasize patient safety and quality of care. Nurses need access to easily understood information about frailty and nursing care implications to accelerate adoption of best practices.

Interdisciplinary learning opportunities in nursing education builds on a strong tradition in geriatric nursing and medicine on the vital role of interdisciplinary team collaborations in addressing the complex needs of older adults, especially those who are frail. The IOM and the Carnegie Report emphasize interdisciplinary collaboration as an essential element in contemporary health care that contributes to improved inpatient care and transitions in care that reduce hospital length of stay and readmission (IOM, 2001; Benner et al., 2010; Gilliss, 2011). Nurse educators must increase education in prelicensure and continuing education programs to prepare registered nurses in clinical

leadership skills to facilitate interdisciplinary collaboration and care coordination in the care of frail adults (Byram, 2001; Gilliss, 2011; Lekan, 2009; Lekan et al., 2010; McConnell, Lekan, Bunn, Egerton, Corazzini, Hendrix, & Bailey, 2009; Pfaff, 2002).

The high level of comorbidity and symptoms in the study sample warrants increased attention in nursing education on symptom management. Symptoms co-occur across multiple diseases and interact in ways that intensify the symptom experience. Treating symptoms one at a time is unlikely to yield the best outcomes since symptoms are not neatly traced to one diagnosis, and treatment of one symptom may have an adverse effect on another (T. E. Seeman, Guralnik, Kaplan, Knudson, & Cohen, 1989; Whitson et al., 2009, 2011). Therefore, symptom management must include comprehensive symptom assessment that considers how symptoms interact in order to determine approaches most likely to be effective. Attention in nursing education on pharmacologic interventions for pain management needs to be balanced by a focus on evidence-based non-pharmacologic pain relieving strategies. Nursing education would contribute to improved care of frail adults by shifting the focus and mental model of frailty as a state of irreversible decline leading to death to a complex physiologic state that is multifactorial, and thus amenable to interventions such as symptom management that would improve comfort, function, and quality of life.

Proactive nursing care could improve prevalent and incident frailty and reduce adverse outcomes. Concerns about the preparedness of the health care workforce in care of the elderly compels greater rigor in prelicensure and continuing nursing education in geriatric nursing (IOM, 2008). Educational programs to enhance geriatric nursing

expertise would improve the clinical reasoning and decision-making in the care of frail adults and appropriately educate patients and families about frailty risk factor reduction, chronic disease and symptom management, and strategies to reduce preventable or inappropriate hospitalization (Ingold et al., 2000; IOM, 2011). There are exemplars for delivery of geriatric nursing content in novel, relevant, and feasible ways in prelicensure and continuing nursing education programs (Barba & Fay, 2009; Barba & Gendle, 2006; Hancock et al., 2006; Kowlowitz, Davenport, & Palmer, 2009; Lekan, 2009; Lekan et al., 2010; McConnell et al., 2009).

### **Clinical Practice**

Nursing's adoption in clinical practice of frailty assessment, risk stratification, primary and secondary prevention, and intervention will be imperative in order to provide high quality, person-centered care that minimizes risk for frailty and its adverse consequences. In this study, many hospitalized adults 55 years of age and older had higher Frailty Scores. In many cases, unrecognized vulnerability based on subjective assessment and younger age exposes high risk hospitalized adults to unnecessary risk since appropriate assessments and interventions would not be implemented. Standard risk assessments for falls, pain, nutrition, delirium, and pressure ulcers, for example, provide a narrow, condition-specific risk profile that may not reflect the intersection and interaction of multiple risk factors in association with comorbidity that magnify risk for frailty (C. C. Chen et al., 2011; Inouye et al., 2007; Quinlan et al., 2011; Potts et al., 1993; Rozzini, et al., 2000; Sager & Rundberg, 1998; Sorace et al., 2011; Thornlow et al., 2009). The Frailty Score in this study included frailty components found in risk assessment tools for

common conditions that occur in hospitalized adults (falls, delirium, pressure ulcers, incontinence, pain). Frailty reflects an advanced stage of vulnerability not captured in individual focused risk assessments performed for these syndromes in hospital settings. Elements of comprehensive geriatric assessment (CGA) that focus on BPSS domains can also be integrated into nursing assessment, such as selected standardized tests for physical and cognitive function. Registered nurses document volumes of clinical data about health and BPSS status. Data generated from multiple sources of information can be aggregated and strategically used in care planning. Development of informatics systems and algorithms to facilitate these processes using data from the EMR would make use of the volume of clinical data that is present in the EMR but not integrated for purposes such as estimating frailty risk and identifying appropriate targeted interventions.

Awareness of the hazards of hospitalization needs to emphasize how conventional care processes contribute to iatrogenesis, geriatric syndromes, functional decline, and frailty (Anpalahan & Gibson, 2007; Creditor, 1993; Lin et al., 2010; Mahoney, 1998; Mahoney, Sager, & Jalalddin, 1988; Mitty, 2010; Olson, Johnson, & Thompson, 1990; Potts et al., 1993; Quinlan et al., 2011). Restricted mobility and limited physical activity is common in acutely ill adults, especially older adults with mobility and cognitive impairment. Immobility has profound adverse effects on physiologic, biopsychosocial, and physical function that increases risk for frailty. Integration of in-bed range of motion and isometric exercise and early mobilization plus physical and occupational therapy as indicated may prevent patients being discharged in worse physical condition despite resolution of medical problems (Arora, Plein, Chen, Siddique, Sachs, & Meltzer, 2009;

2009; Ávila-Funes et al., 2011; Boltz et al., 2012; C. J. Brown et al., 2004, 2009; Gill, Allore, et al., 2010).

Chronic pain is an important frailty risk factor. In the hospital setting, acute pain may command greater attention than chronic pain and may be under-treated (Maxwell et al., 2008). Decline in functional status especially related to pain during hospitalization can be long-lasting and impact frailty (Boyd et al., 2005; C. J. Brown et al., 2004, 2007, 2009; Graf, 2006). Alleviation of chronic pain may facilitate mobility and recovery and reduce risk for or severity of frailty (Pine et al., 2000; Winograd, Gerety, Brown, & Kolodny, 1988).

Research indicates that frailty is a dynamic state with fluctuations in level of frailty (Campbell & Buckner, 2007; Fried et al., 2009; Lipsitz, 2004; Puts et al., 2005). Frailty assessment on admission, during hospitalization, and at discharge would provide useful information about baseline status, the impact of acute illness and hospitalization on homeostasis, compensatory reserve, and recovery, and changes that warrants attention. This information would be critical in discharge planning, care coordination, referral, and strategic planning with family and other caregivers (Duke, 2005; K. E. Covinsky et al., 2003; Horwitz, 2012; Naylor, Kurtzman, Grabowski, Harrington, McClellan, & Reinhard, 2012; Winograd et al., 1988). Education and evidence-based policies and procedures for symptom management, palliative care, and end-of-life care is needed to facilitate appropriate goal setting in later stages of frailty (Gill, Gabhauer, et al., 2010; Nicholson, Meyer, Flatley, Holman, & Lowton, 2012; Raudonis & Daniel, 2010).

Interdisciplinary communication and collaboration is essential in the care of hospitalized frail adults. The complex, multidimensional nature of frailty compels dynamic interaction among care providers. Interdisciplinary team members perform discipline-focused standardized assessments that yield crucial information about health status, and actual and potential problems. However, these focused assessments may not fully capture the BPSS vulnerability associated with frailty. Frailty assessment initiated by the RN that integrates interdisciplinary assessment data would provide a comprehensive database for risk stratification and targeted prevention and intervention.

A critical element of RN leadership would be to facilitate interdisciplinary communication, care coordination, and discharge planning to facilitate optimal inpatient care and appropriate transitions in care and referral. Nursing models to enhance quality of care require nursing leadership to ensure collaborative interdisciplinary teamwork in the care of frail elderly (E. Chang, Hancock, Hickman, Glasson, & Davidson, 2007; Duke, 2005; Fitzpatrick, Salinas, et al., 2004; Winograd et al., 1988). Models of care to improve geriatric care in hospital settings such as NICHE (Nurses Improving Care of HealthSystem Elders), ACE (Acute Care for Elders) units, and the use of standardized geriatric syndrome assessment tools in clinical care have slowly been adopted by health systems (Boltz et al., 2008a, 2008b; Counsell et al., 2000; Jayadevappa, Bloom, Raziano, & Lavizzo-Mourey, 2003; Mezey et al., 2004; Mezey & Mitty, 2011; Palmer, Counsell, & Landefeld, 1998; Panno, Kolcaba, & Holder, 2000). These program initiatives have demonstrated improvements in quality of care and outcomes for older adults but widespread adoption has been slow and sustaining programs difficult. RN leadership at

all levels of the organization is critical in initiating and sustaining these models. Proactive engagement with interdisciplinary team members could improve the quality and sustainability of these programs. By taking an active role in monitoring systematic and consistent implementation and evaluation of frailty assessment and care delivery, nursing provides a valuable linkage for interdisciplinary teamwork that could hasten recovery and reduce hospital-acquired adverse events, poor outcomes, length of stay and readmission (Barba & Gendle, 2006; Lekan et al., 2010; McConnell et al., 2009; Pfaff, 2002; Winograd et al., 1988).

### **Research**

Further research is needed using advanced analytic procedures such as factor analysis, correspondence analysis, and other models to evaluate the frailty components and indicator variables for the Frailty Score. Additional demographic and BPSS variables should be examined as frailty components. Development and testing of frailty screening tools and multidimensional frailty assessments for those who screen positive is needed (Rockwood & Bergman, 2012). Before widespread use, validation of these instruments should be conducted in hospital settings that vary by size, ownership, location, service population, nursing practice models and staffing, and medical, surgical, and specialty services (Perera et al., 2010). The value of geriatric nursing expertise and role the clinical nurse specialist should be evaluated (Boltz et al., 2008a; 2008b; Fitzpatrick, Salinas, et al., 2004; Fulmer et al., 2002; Mezey et al., 2004).

The relative contribution of each biomarker as a component of the Frailty Score requires further analysis. Research is needed to determine the added value of CRP or hs-

CRP in frailty assessment since it is not commonly ordered in hospitalized adults.

Consensus conferences and research have yet to identify which biomarkers, number of biomarkers, or combination of biomarkers best characterize frailty in hospitalized adults who are acutely ill. Inclusion of other biomarkers such as creatinine, fasting glucose, glycosylated hemoglobin, lipids (cholesterol, LDL, HDL, lipid ratios), cortisol, epinephrine, norepinephrine, and others that are associated with chronic inflammation, malnutrition, and frailty should be considered in light of their relevance, feasibility, and cost in the hospital setting and any potential burden to patients.

In this study, the abnormal flag for biomarkers was used as a categorical variable in analyses. Prior research in community medically-stable older adults examining multiple biomarkers found that even marginally abnormal values above or below the reference was predictive of frailty as the numbers of marginally abnormal biomarkers increased (Gruenewald et al., 2006; Puts et al., 2005). A larger aggregate of marginally abnormal biomarkers signaled an increased level of global physiologic instability and vulnerability. In hospitalized acutely ill adults, the use of abnormal flags for biomarkers may not be sufficient. Thus, future research should analyze plasma values to determine if there are thresholds that more precisely differentiate risk.

Longitudinal research is needed to describe the etiologies, precursors, risk factors, natural history, and trajectories of frailty in hospitalized adults 55 years of age and older. A better understanding is needed about subtypes or dimension of frailty and differences in frailty trajectories in hospitalized adults experiencing acute illness, surgery, and BPSS stressors (Puts et al., 2005; Sarkisian et al., 2008; Sourial et al., 2010). This would help

determine the most appropriate assessments and interventions and when they are most likely to be effective (Cesari, 2011b; Newman et al., 2001; Whitson et al., 2007). Future studies should assess pre-hospital BPSS status and frailty on admission, during hospitalization, and post hospitalization. Investigation of health system processes that contribute to prevalent and incident frailty is needed.

Research on educational and clinical practice improvement models to disseminate knowledge about frailty in hospitalized adults is needed. The proportion of hospitalized adults who are 65 years of age and older has increased over the past few decades and is estimated at over 50% with higher rates on medical units (Sonnenblick et al., 2007). Advancing age is accompanied by diversity in comorbidity and BPSS function thus goals and treatment should be considered in light of risk for frailty and geriatric syndromes. Preventing frailty, functional decline, and geriatric syndromes requires a workforce with geriatric expertise which is insufficient in many hospital settings (Mezey et al., 2004; Mezey & Fulmer, 1998). Research on methods and models for interdisciplinary collaboration to address frailty and geriatric syndromes is needed since the inter-relationships of these conditions require interdisciplinary expertise (Conroy, Stevens, Parker, & Gladman, 2010).

Qualitative and mixed methods studies are needed to explore perception of frailty and its natural history in hospitalized adults from the perspective of frail individuals and health care providers (Nicholson, Meyer, Flatley, & Holman, 2012; Lindhardt, Hallberg, & Poulsen, 2008). Much of the qualitative research on frailty is from disciplines related to, gerontology, medicine, women's studies, anthropology, social sciences, and

psychology (Becker, 1994; Chater, 2002; Gealey, 1997; Gray, 1998; Grenier, 2002; Grenier & Hanley, 2007; Jett, 1994; Kaufman, 1994; van Kempen et al., 2012). Nursing research on frailty is desperately needed since nurses are frontline care providers in frequent contact with frail adults across care settings. Little is known about effective nurse *caring* behaviors for frail adults (Erlen, 2007; Gealey, 1997; Lekan, 2009; Lindhardt et al., 2008). Care preferences at different stages of frailty need to be explored with frail adults and caregivers as indicated. Nursing research is needed since little is known about how nursing can anticipate needs and negotiate discussions about care preferences. There is evidence that frail older adults need support in maintaining the balance of accumulated losses and sustaining and creating new ways to maintain connections between personal experience and routines, social relationships, and the environment (Becker, 1994; Nicholson, Meyer, Flatley, & Holman, 2012; Nicholson, Meyer, Flatley, Holman, & Lowton, 2012). Home care focused on psychosocial issues and person-centered care instead of medical treatment and cure promotes better provider-client relationships and quality of life as frailty progresses (Horowitz, 1985; Nicholson, Meyer, Flatley, Holman, & Lowton, 2012; van Kempen et al., 2012).

There is evidence of stigma associated with the diagnostic label of frailty (Becker, 1994; Chater, 2002; Fillit & Butler, 2009; Gray, 1998; Grenier, 2002; Grenier & Hanley, 2007; Jett, 1994; Kaufman, 1994; Palmore, 2004). Qualitative research describes aversion to the term frailty or frail when that label is used to by health professionals to describe that person's health status. Studies report discordance between health professional perspectives of frailty and perspectives held by persons who have consciously made

lifestyle adaptations to diminishing resilience and function. The over-medicalization of frailty has been cited as a barrier to productive discussions about living well in the context of frailty and associated morbidity, disability, and symptoms. Nursing research is needed to determine how socially constructed meanings about frailty that conflicts with personal experience have an impact on health status, lifestyle behaviors, and emotional well-being that influence risk for frailty (Becker, 1994; Chater, 2002; Gray, 1998; Grenier, 2002; Kaufman, 1994). Such research would address a void in the literature about best practices at different stages of frailty and reframe perspectives to facilitate person-centered care and interventions that focus on personal goals, caregiving and treatment preferences, symptom management, and discussions about what constitutes a good death (Gallagher, 2013; Kehl, 2006; Raudonis, & Daniel, 2010).

Research is needed to articulate the leadership role of the RN in frailty assessment and in facilitating interdisciplinary communication, collaboration, and care coordination (Fulmer et al., 2002; Lekan et al., 2010; Pfaff, 2002). Incorporation of frailty assessment in the nursing process and using the EMR data in collaboration with the interdisciplinary team more strategically would improve patient and organizational outcomes.

### **Public Policy**

Frailty has entered the national health care agenda. As part of the Affordable Care Act, the CMS issued guidelines focused on reducing unplanned, preventable hospital readmissions that are linked to benchmarking of hospital performance and penalties that reduce payment to hospitals with excess readmissions (CMS, 2012a, 2012b; Kautter et al., 2008–2009). Hospital's readmission performance is compared to the national average

for patients with certain conditions adjusted for patient demographics, comorbidities, and patient frailty (CMS, 2012b). Based on prior work with risk models used for Managed Care Organizations such as PACE, CMS determined that diagnosis-based risk adjustments do not provide the most accurate prediction of expenditures associated with care of frail elderly. CMS defines frailty in terms of functional impairments with a focus on ADL function (Kautter et al., 2008–2009). CMS acknowledges frailty research that describes the biologic, phenotype of frailty and its clinical features of weight loss, weakness, fatigue, inactivity, low nutrient, sarcopenia, abnormal gait and balance, and decreased bone mass. Although CMS recognized the complexity of the frailty syndrome, ADL function was determined as the primary element in risk adjustment formulas based on prior research on its validity in risk models. CMS regulations levy fiscal penalties for preventable events that occur during hospitalization and for 30-day readmission. Since level of frailty is part of the risk adjustment formula, mobilization of resources to define frailty that adheres to CMS guidelines and incorporates additional evidence-based BPSS predictors to address multidimensional aspects of frailty, especially those amenable to intervention, would enhance quality of care. Frailty definition should not be limited to chronologic age as defined by CMS (65 years of age and older), given findings from the present study and other literature on frailty in adults under 65 years of age.

Stipulations in the Affordable Care Act related to the Hospital Readmissions Reduction Program for three chronic conditions (heart failure, pneumonia, acute myocardial infarction) may have unintended consequences for older adults who need long term health and social services and other supports. Although designed to reduce

fragmented care and poor communication and improve transitions in care for chronic disease management, Naylor et al. (2012) found that the provisions in the Affordable Care Act inadequately addressed the unique needs of subgroups of vulnerable elders. Frail older adults experience fluctuations in health status, have multiple providers, and undergo frequent transitions in care (hospital, home health, rehabilitation, nursing home). There is lack of integration and inadequate numbers and types of community resources to meet the needs of chronically ill older adults. In contrast, an unintended consequence is that since only three diagnoses are subject to the 30-day readmission penalty, readmission for other diagnoses is likely to continue since reimbursement from these admissions more than offset the fiscal penalty. Naylor and colleagues (2012) recommend that policy makers anticipate unintended consequences and advance payment policies that integrate care and support providers in implementing evidence-based transitional care practices and integrate measurement and reporting requirements into performance systems. The primary goal is for older adults to achieve better health outcomes through a more rational, organized, and integrated health system that promotes stability in chronic disease management and reduces costs due to preventable health care resource utilization.

An important policy issue is for frailty to be designated an ICD-10 code with diagnostic criteria. Failure-to-thrive (FTT) has an ICD-9/10 code, although this condition lacks substantive research and is poorly defined. The code for FTT may be used by default for frailty. An ICD-10 code for frailty is needed so health care providers can provide an accurate diagnostic label in order to assess the health status of populations and track clinical data at the individual and aggregate level. Administrative databases could

also track financial data related to frailty within health care settings and across the health system to monitor resource utilization, care processes and quality, costs, and other outcomes.

National and local initiatives are needed to develop information technology systems to integrate frailty assessment, risk stratification, and primary and secondary prevention and treatment into the EMR with decision-prompts to facilitate adoption of best practices for optimal patient and system-level outcomes. Using informatics technology, decision trees, and algorithms to synthesize information from frailty assessment would facilitate the use of relevant information from interdisciplinary assessments and contribute to development of evidence-based care plans for frail adults. Methods for data tracking and analysis would permit timely appraisal of clinical information that could guide care management and early detection of untoward events.

### **Chapter Summary**

Frailty was examined in this cross-sectional, descriptive, retrospective study in 278 hospitalized adults 55 years of age and older admitted to an internal medicine, cardiology, or orthopedic unit at a large academic medical center. Frailty was characterized by a Frailty Score consisting of 14 evidence-based frailty components defined by 26 indicator variables from data available in the EMR. The majority of frailty research has been conducted in medically-stable community-living older adults. There is scarce research on frailty in acutely ill hospitalized adults.

In the present study, the Frailty Score mean and range was similar across age tertiles with a modest increase in the Frailty Score with age. Frailty indicators were

identified in midlife adults not expected to be at risk for frailty or to be frail. Thus, a need exists to examine frailty in hospitalized adults 55 years of age and older to enhance early detection, primary and secondary prevention, and palliative and end-of-life care, and facilitate appropriate transitions in care.

Most definitions of frailty describe it as a geriatric syndrome that evolves as part of the aging process, manifests in the aged who have medical problems and/or disability, and frequently occurs in the very old and terminally ill. Clinicians report that frailty is often readily observable based on intuitive, subjective assessment (Rockwood et al., 2005; Studenski et al., 2004). In this study, few physicians documented a diagnosis or clinical impression of frailty, or the related construct, failure-to-thrive. These terms often described the fragile appearance and tenuous health status of an older patient. That a high number of frailty components were identified in adults 55 to 64 years of age contrast with prevailing conceptions of frailty as a geriatric syndrome that affects the very old.

In the present study, frailty was defined using multidimensional, BPSS components. The integration of multiple domains of human functioning in the conceptualization of frailty underscores the inter-relatedness of these domains in health and illness and the complexity introduced by aging changes, multiple morbidity, symptoms, and functional limitations (Abellan van Kan et al., 2010; I. Brown et al., 1995; Ferrucci et al., 2004; Gobbens et al., 2010c; Rockwood & Bergman, 2012). This view is gaining greater acceptance in comparison to the two dominant frailty definitions, the biologic model (Fried, Tangen, et al., 2001) and the deficit accumulation model (Rockwood & Mitnitski, 2011), which are more challenging to implement and provide

limited guidance for frailty prevention and intervention. Consensus conference recommendations and expert opinion encourage clinicians to “look at patients as whole people and not just as a single illness” (Rockwood & Bergman, 2012, p. 35). This perspective is relevant to care delivery in hospital settings since patients are admitted for a primary problem and assigned a primary service yet it is unlikely that only one medical problem will require monitoring and intervention. Instability in one physiologic area begets instability across body systems. Given the study sample characteristics that point to high acuity and complexity of care, the role of nursing in assuming leadership in frailty assessment and interdisciplinary team communication, collaboration, and care coordination is compelling in order to effectively and favorably impact health status outcomes, hospital length of stay, and readmission.

In this study, the Frailty Score was significantly associated with longer length of stay but not 30-day hospital readmission. Although research indicates that frailty status is significantly associated with longer length of stay, data about admissions from dependent care settings such as skilled nursing facilities and assisted living were not analyzed. Research indicates that this population has higher hospitalization and readmission rates compared to independent living older adults (Fried & Mor, 1997; Ouslander & Berenson, 2011). The study sample was constructed to include admissions that had laboratory data for four biomarkers related to inflammation, malnutrition, and frailty. These criteria may differentiate this sample as more acutely ill and vulnerable to longer length of stay.

Research indicates that many unplanned hospital readmissions are preventable (Dasgupta et al., 2009; Hilmer, Perera, et al., 2009; Ingold et al., 2000; Jencks, Williams,

& Coleman, 2009). Reasons for hospital readmission were outside the scope of this study. Many factors influence hospital readmission: new acute illness, chronic disease exacerbation, lack of effective discharge planning and follow-up, discharge before medically stable, no access to a primary care provider, and lack of preparedness of caregivers in the home or dependent care setting to recognize significant change in the patient's condition so the provider can be notified, treatment initiated, and hospitalization prevented (Fried & Mor, 1997; Ouslander & Berenson, 2011).

The present study was a preliminary descriptive investigation of frailty in hospitalized adults 55 years of age and older admitted to medicine services to address a lack of scientific knowledge and substantive research to guide practice in this setting at a time when the demographics of the U.S. aging population predict increased health care needs and utilization. Translation of existing knowledge and frailty assessment tools from research conducted in medically stable, community-living older adults to acutely ill adults in the hospital setting has limited utility and questionable validity and presents barriers to implementation in practice. The present study incorporated validated frailty components and biomarkers to characterize a sample of hospitalized adults where higher Frailty Scores were documented across age tertiles. There is ample evidence from this study for continued investigations to identify components of a clinically-relevant, practical, and feasible frailty assessment instrument for use in clinical practice that considers the unique characteristics of acutely ill hospitalized adults.

## REFERENCES

- Abellan van Kan, G., Rolland, Y., Andrieu, S., Bauer, J., Beauchet, O., Bonnefoy, M., . . . Vellas, B. (2009). Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people: An international academy of nutrition and aging (I.A.N.A.) task force. *Journal of Nutrition, Health & Aging, 13*(10), 881–889.
- Abellan van Kan, G., Rolland, Y., Bergman, H., Morley, J. E., Kritchevsky, S. B., & Vellas, B. (2008). The I.A.N.A Task Force on frailty assessment of older people in clinical practice. *Journal of Nutrition in Health & Aging, 12*(1), 29–37.
- Abellan van Kan, G., Rolland, Y., Houles, M., Gillette-Guvonnet, S., Soto, M., & Vellas, B. (2010). The assessment of frailty in older adults. *Clinics in Geriatric Medicine, 26*(2), 275–286.
- Abellan van Kan, G., Rolland, Y. M., Morley, J. E., & Vellas, B. (2008). Frailty: Toward a clinical definition. *Journal of the American Medical Directors Association, 9*(2), 71–72. doi:10.1016/j.jamda.2007.11.005
- Adams, K., & Corrigan, J. M. (Eds.). (2003). *Priority areas for national action: Transforming health care quality*, Washington, DC: National Academies Press.
- Adler, R. H. (2009). Engel's biopsychosocial model is still relevant today. *Journal of Psychosomatic Research, 67*(6), 607–611.
- Afilalo, J., Eisenberg, M. J., Morin, J. F., Bergman, H., Monette, J., Noiseux, N., . . . Bovin, J. F. (2010). Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *Journal of the American College of Cardiology, 56*(20), 1668–1676. doi:10.1016/j.jacc.2010.06.039
- Afilalo, J., Karunanathan, S., Eisenberg, M. J., Alexander, K., & Bergman, H. (2009). The role of frailty in patients with cardiovascular disease. *American Journal of Cardiology, 103*(11), 1116–1121.
- Afilalo, J., Mottillo, S., Eisenberg, M. J., Alexander, K. P., Noiseux, N., Perrault, L.P., . . . Bergman, H. (2012). Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circulation. Cardiovascular Quality and Outcomes, 5*(2), 222–228. doi:10.1161/CIRCOUTCOMES.111.963157

- Aggar, C., Ronaldson, S., & Cameron, I. (2011). Reactions to caregiving in frailty research. *Archives of Gerontology & Geriatrics, 53*(2), e138–e143. doi:10.1016/j.archger.2010.07.010
- Ahmed, N., Mandel, R., & Fain, M. J. (2007). Frailty: An emerging geriatric syndrome. *The American Journal of Medicine, 120*(9), 748–753. doi.org/10.1016/j.amjmed.2006.10.018
- Ahmed, N. N., Sherman, S. J., & Vanwyck, D. (2008). Frailty in Parkinson's disease and its clinical implications. *Parkinsonism and Related Disorders, 14*(4), 334–337.
- Albert, S. M., Im, A., & Raveis, V. H. (2002). Public health and the second 50 years of life. *American Journal of Public Health, 92*(8), 1214–1216.
- Alexander, N. B., Taffet, G. E., McFarland Horne, F., Eldadah, B. A., Ferrucci, L., Nayfield, S., & Studenski, S. (2010). Bedside-to-bench conference: Research agenda for idiopathic fatigue and aging. *Journal of the American Geriatrics Society, 58*(5), 967–975. doi:10.1111/j.1532-5415.2010.02811
- Alley, D. E., Seeman, T. E., Kim, K., Karlamangla, A., Hu, P., & Crimmons, E. M. (2006). Socioeconomic status and c-reactive protein levels in the US population: NHANES IV. *Brain, Behavior, and Immunity, 20*(5), 498–504.
- Almeida, O. P., Garrido, G. J., Lautenschlager, N. T., Hulse, G. K., Jamrozik, K., & Flicker, L. (2008). Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease. *American Journal of Geriatric Psychiatry, 16*(1), 92–98. doi:10.1097/JGP.0b013e318157cad2
- Almeida, O. P., Norman, P. E., van Bockxmeer, F. M., Hankey, G. J., & Flicker, L. (2012). CRP 1846G: A polymorphism increases risk of frailty. *Maturitas, 71*(3), 261–266.
- Alvarado, B. E., ZunZuneui, M. V., & Béland, R. (2008). Life course social and health conditions linked to frailty in Latin American older men and women. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 63*(12), 1399–1406.
- American Association of Colleges of Nursing (AACN). (2011a). AACN "Essentials" series. Retrieved from <http://www.aacn.nche.edu/Education/essentials.htm>
- American Association of Colleges of Nursing (AACN). (2011b). *Geriatric nursing education project*. Retrieved from <http://www.aacn.nche.edu/education/hartford/index.htm>

- AmericanFactFinder. (2012). *U.S. population clock*. U.S. Census Bureau. Retrieved from [http://factfinder.census.gov/servlet/ACSSAFFacts?\\_submenuId=factsheet\\_1&\\_sse=on](http://factfinder.census.gov/servlet/ACSSAFFacts?_submenuId=factsheet_1&_sse=on)
- American Medical Association (AMA). (1990). American medical association white paper on elderly health. Report of the council of scientific affairs. *Archives of Internal Medicine*, *150*(12), 2459–2472.
- American Medical Association (AMA). (2013). Obesity as a disease. Retrieved from <http://www.ama-assn.org/ama/home.page?>
- Andrew, M. K., Mitnitski, A. B., & Rockwood, K. (2008). Social vulnerability, frailty and mortality in elderly people. *PLoS ONE*, *3*(5), e2332. doi:10.1371/journal.pone.0002232
- Anpalahan, M., & Gibson, S. J. (2007). Geriatric syndromes as predictors of adverse outcomes of hospitalization. *Internal Medicine Journal*, *38*(1), 16–23.
- Arora, V. M., Plein, C., Chen, S., Siddique, J., Sachs, G. A., & Meltzer, D. O. (2009). Relationship between quality of care and functional decline in hospitalized vulnerable elders. *Medical Care*, *47*(8), 895–901.
- Arques, S., Roux, E., Sbragia, P., Gelisse, R., Pieri, B., & Ambrosi, P. (2008). Usefulness of serum albumin concentration for in-hospital risk stratification in frail, elderly patients with acute heart failure. Insights from a prospective, monocenter study. *International Journal of Cardiology*, *125*(2), 265–267.
- Artz, A. S., & Thirman, M. J. (2011). Unexplained anemia predominates despite an intensive evaluation in a racially diverse cohort of older adults from a referral anemia clinic. *The Journals of Gerontology. Series A, Biological Science and Medical Sciences*, *66*(8), 925–932. doi:10.1093/gerona/glr090
- Ávila-Funes, J. A., Amieva, H., Barberger-Gateau, P., Le Goff, M., Raoux, N., Ritchie, K., . . . Dartigues, J. F. (2009). Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: The three-city study. *Journal of the American Geriatrics Society*, *57*(3), 453–461.
- Ávila-Funes, J. A., Pina-Escudero, S. D., Aguilar-Navarro, S., Gutierrez-Robledo, L. M., Ruiz-Arregui, L., & Amieva, H. (2011). Cognitive impairment and low physical activity are the components of frailty more strongly associated with disability. *Journal of Nutrition, Health, & Aging*, *15*(8), 683–689.

- Avlund, K., Damsgaard, M. T., Sakari-Rantala, R., Laukkanen, P., & Schroll, M. (2002). Tiredness in daily activities among nondisabled old people as determinant of onset of disability. *Journal of Clinical Epidemiology*, *55*(10), 965–973.
- Avlund, K., Hokland, M., Mehlsen, M. Y., Thomsen, D. K., Viidik, A., Ekmann, A., & Zachariae, R. (2012). Differential associations between white blood cell counts and fatigue in young and older adults. *Aging, Clinical, and Experimental Research*, *24*(5), 439–347. doi:10.3275/8473
- Avlund, K., Rantanen, T., & Schroll, M. (2006). Tiredness and subsequent disability in older adults: The role of walking limitations. *Journals of Gerontology. Series A, Biologic Sciences and Medical Sciences*, *61*(11), 1201–1205.
- Avlund, K., Rantanen, T., & Schroll, M. (2007). Factors underlying tiredness in older adults. *Aging, Clinical, and Experimental Research*, *19* (1), 16-25.
- Balducci, L., & Stanta, G. (2000). Cancer in the frail patient: A coming epidemic. *Hematology Oncology Clinics of North America*, *14*(1), 235–250.
- Bales, C. W., & Ritchie, C. S. (2002). Sarcopenia, weight loss, and nutritional frailty in the elderly. *Annual Review of Nutrition*, *22*, 309–323.
- Ballard, J., Mooney, M., & Dempsey, O. (2013). Prevalence of frailty-related risk factors in older adults seen by community nurses. *Journal of Advanced Nursing*, *69*(3), 675–684. doi:10.1111/j.1365-2648.2012.06054.x
- Bandeem-Roche, K., Walston, J. D., Huang, Y., Semba, R. D., & Ferrucci, L. (2009). Measuring systemic inflammatory regulation in older adults: Evidence and utility. *Rejuvenation Research*, *12*(6), 403–410. doi:10.1089=rej.2009.0883
- Bandeem-Roche, K., Xue, Q.L., Ferrucci, L., Walston, J., Guralnik, J.M., & Fried, L.P. (2006). Phenotype of frailty: Characterization in the women’s health and aging studies. *Journals of Gerontology. Series A, Biologic Sciences and Medical Sciences*, *61*(3), 262–266.
- Bandinelli, S., Corsi, A. M., Milaneschi, Y., & Vazzana, R. (2010). Frailty and the homeostatic network. *Acta Bio-medica*, *81*(Suppl. 1), 15–18.
- Bao, A. M., Meynen, G., & Swaab, D. F. (2008). The stress system in depression and neurodegeneration: Focus on the human hypothalamus. *Brain Research Review*, *57*(2), 531–553.
- Barba, B. E., & Fay, V. (2009). Does continuing education in gerontology lead to changes in nursing practice? *Journal of Gerontological Nursing*, *35*(4), 11–17.

- Barba, B. E., & Gendler, P. (2006). Education/community collaborations for undergraduate nursing gerontological clinical experiences. *Journal of Professional Nursing, 22*(2), 107–111.
- Bartali, B., Frongillo, E. A., Bandinelli, S., Lauretani, F., Semba, R. D., Fried, L. P., & Ferrucci, L. (2006). Low nutrient intake is an essential component of frailty in older persons. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 61*(6), 589–593.
- Barzilay, J. I., Blaum, C., Moore, T., Xue, Q. L., Hirsch, C. H., Walston, J. D., & Fried, L. P. (2007). Insulin resistance and inflammation as precursors of frailty: The cardiovascular health study. *Archives of Internal Medicine, 167*(7), 635–641.
- Bassuk, S. S., Fifai, N., & Ridker, P. M. (2004). High-sensitivity c-reactive protein: Clinical importance. *Current Problems in Cardiology, 29*(8), 439–493.  
doi:10.1016/j.cpcardiol.2004.03.004
- Bautmans, I., Njemini, R., Lambert, M., Demanet, C., & Mets, T. (2005). Circulating acute phase mediators and skeletal muscle performance in hospitalized geriatric patients. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 60*(3), 361–367.
- Beck, F. K., & Rosenthal, T. C. (2002). Prealbumin: A marker for nutritional evaluation. *American Family Physician, 65*(8), 1575–1578.
- Becker, G. (1994). The oldest old: Autonomy in the face of frailty. *Journal of Aging Studies, 8*(1), 59–76.
- Beeson, T., Adams, G., Prickel, C., Treon, M. L., Mink, J., & Buelow, J. M. (2010). Thinking about the braden scale. *Clinical Nurse Specialist, 24*(2), 49–50.  
doi:10.1097/NUR.0b013e3181d25205
- Benner, P., Sutphen, M., Leonard, V., & Day, L. (2010). *Educating nurses. A call for radical transformation*. The Carnegie Foundation for the Advancement of Teaching. San Francisco, CA: Jossey-Bass.
- Berardelli, M., De Rango, F., Morelli, M., Corsonello, A., Mazzei, B., Mari, V., . . . Passarino, G. (2013). Urinary incontinence in the elderly and in the oldest old: Correlation with frailty and mortality. *Rejuvenation Research, 16*(3), 206–211.  
doi:10.1089/rej.2013.1417
- Bergman, H., Ferrucci, L., Guralnik, J., Hogan, D. B., Hummel, S., Karunanathan, S., & Wolfson, C. (2007). Frailty: An emerging research and clinical paradigm—issues

and controversies. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7), 731–737.

Bergstrom, N., & Braden, B. J. (2002). Predictive value of the braden scale among black and white subjects. *Nursing Research*, 51(6), 398–403.

Bergstrom, N., Demuth, P. J., & Braden, B. J. (1987). A clinical trial of the Braden Scale for predicting pressure sore risk. *Nursing Clinics of North America*, 22(2), 417–428.

Bergstrom, N., Braden, B., Kemp, M., Champagne, M., & Ruby, E. (1998). Predicting pressure ulcer risk: A multisite study of the predictive validity of the Braden Scale. *Nursing Research*, 47(5), 261–269.

Bergstrom, N., Braden, B. J., Laguzza, A., & Holman, V. (1987). The Braden Scale for predicting pressure sore risk. *Nursing Research*, 36(4), 205–210.

Berkman, B., Foster, L. W., & Champion, E. (1989). Failure to thrive: Paradigm for the frail elder. *Gerontologist*, 29(5), 654–659.

Berman, P., Hogan, D. B., & Fox, R. A. (1987). The atypical presentation of infection in old age. *Age & Aging*, 16(4), 201–207.

Beutler, E., & Waalen, J. (2006). The definition of anemia: What is the lower limit of normal of the blood hemoglobin concentration? *Blood*, 107(5), 1747–1750. doi:10.1182/blood-2005-07-3046

Bilotta, C., Casè, A., Nicolini, P., Mauri, S., Castelli, M., & Vergani, C. (2010). Social vulnerability, mental health and correlates of frailty in older outpatients living alone in the community in Italy. *Aging & Mental Health*, 14(8), 1024–1036.

Blaum, C. S., Xue, Q. L., Michelon, E., Semba, R. D., & Fried, L. P. (2005). The association between obesity and the frailty syndrome in older women: The women's health and aging studies. *Journal of the American Geriatrics Society*, 53(6), 927–934.

Blaum, C. S., Xue, Q. L., Tian, J., Semba, R. D., Fried, L. P., & Walston, J. (2009). Is hyperglycemia associated with frailty status in older women? *Journal of the American Geriatrics Society*, 57(5), 840–847.

Blyth, R. M., Rochat, S., Cumming, R. G., Creasey, H., Handelsman, D. J., Le Couteur, D. G., . . . Waite, L. M. (2008). Pain, frailty and comorbidity on older men: The CHAMP study. *Pain*, 140(1), 224–230. doi:10.1016/j.pain.2008.08.011

- Bogner, H.R. (2004). Urinary incontinence and psychological distress in community-dwelling older african americans and whites. *Journal of the American Geriatrics Society*, 52(11), 1870-1874.
- Bogner, H. R., & Gallo, J. J. (2004). Urinary incontinence, condition-specific functional loss, and psychological distress. *Journal of the American Geriatrics Society*, 50(7), 1311.
- Bogner, H. R., Gallo, J. J., Sammel, M. D., Ford, D. E., Armenian, H. K., & Eaton, W. W. (2002). Urinary incontinence and psychological distress in community-dwelling older adults. *Journal of the American Geriatrics Society*, 50(3), 489–495.
- Bohannon, R. W., & Williams Andrews, A. (2011). Normal walking speed: A descriptive meta-analysis. *Physiotherapy*, 97(3), 182–189. doi:10.1016/j.physio.2010.12.004
- Bolton, L. (2007). Which pressure ulcer risk assessment scales are valid for use in the clinical setting? *Journal of Wound, Ostomy, Continence Nursing*, 34(4), 368–381.
- Boltz, M., Capezuti, E., Bowar-Ferres, S., Norman, R., Secic, M., Kim, H., . . . Fulmer, T. (2008a). Changes in the geriatric care environment associated with NICHE (nurses improving care for healthsystem elders). *Geriatric Nursing*, 29(3), 176–185.
- Boltz, M., Capezuti, E., Bowar-Ferres, S., Norman, R., Secic, M., Kim, H., . . . Fulmer, T. (2008b). Hospital nurses' perception of the geriatric nurse practice environment. *Journal of Nursing Scholarship*, 40(3), 282–289.
- Boltz, M., Resnick, B., Capezuti, E., Shuluk, J., & Secic, M. (2012). Functional decline in hospitalized older adults: Can nursing make a difference? *Geriatric Nursing*, 33(4), 272–279. doi:10.1016/j.gerinurse.2012.01.008
- Bookwala, J., & Lawson, B. (2011). Poor vision, functioning, and depressive symptoms: A test of the activity restriction model. *Gerontologist*, 51(6), 798–808. doi:10.1093/geront/gnr051
- Borrell-Carrió, F., Suchman, L., & Epstein, R. E. (2004). The biopsychosocial model 25 years later: Principles and scientific inquiry. *Annals of Family Medicine*, 2(6), 576–582. doi:10.1370/afm.245
- Bortz, W. M. (1982). Disuse and aging. *Journal of the American Geriatrics Society*, 248(10), 1203–1208.

- Bortz, W. M. (1989). Redefining human aging. *Journal of the American Geriatrics Society*, 37(11), 1092–1096.
- Bortz, W. M. (1993). The physics of frailty. *Journal of the American Geriatrics Society*, 41(9), 1004–1008.
- Bortz, W. M. (2002). A conceptual framework of frailty: A review. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 57(5), M283–M238.
- Bortz, W. M. (2008). Frailty. *Mechanisms of Ageing and Development*, 129(11), 680.
- Bortz, W. M. (2010). Understanding frailty. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 65(3), 255–256.
- Bowsher, J., Bramlett, M., Burnside, I. M., & Gueldner, S. H. (1993). Methodological considerations in the study of frailty elderly people. *Journal of Advanced Nursing*, 18(6), 878–879.
- Boxer, R. S., Wang, Z., Walsh, S. J., Hager, D., & Kenny, A. M. (2008). The utility of the 6-minute walk test as a measure of frailty in older adults with heart failure. *American Journal of Geriatric Cardiology*, 17(1), 7–12.
- Boyd, C. M., Xue, Q. L., Simpson, C. F., Guralnik, J. M., & Fried, L. P. (2005). Frailty, hospitalization, and progression of disability in a cohort of disabled women. *American Journal of Medicine*, 118(11), 1225–1231.
- Boyle, P. A., Buchman, A. S., Wilson, R. S., Bienias, J. L., & Bennett, D. A. (2007). Physical activity is associated with incident disability in community-based older persons. *Journal of the American Geriatrics Society*, 55(2), 195–201.
- Braun, J. V., Wykle, M. H., & Cowling, W. R. III. (1988). Failure to thrive in older persons: A concept derived. *Gerontologist*, 28(6), 809–812.
- Brinkley, T. E., Leng, X., Miller, M. E., Kitzman, D. W., Pahor, M., Berry, M. J., . . . Nicklas, B. J. (2009). Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 64(4), 455–461.
- Brocklehurst, J. C. (1985). The geriatric service and the day hospital. In J. C. Brocklehurst (Ed.), *Textbook of geriatric medicine and gerontology* (pp. 982–995). Edinburgh: Churchill Livingstone.

- Brody, B. L., Gamst, A. C., Williams, R. A., Smith, A. R., Lau, P. W., Dolnak, D., . . . Brown, S. I. (2001). Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. *Ophthalmology*, *108*(10), 1893–1900.
- Brown, C. J., Friedkin, R. J., & Inouye, S. K. (2004). Prevalence and outcomes of low mobility in hospitalized older patients. *Journal of the American Geriatrics Society*, *52*(8), 1263–1270.
- Brown, C. J., Redden, D. T., Flood, K. L., & Allman, R. M. (2009). The under-recognized epidemic of low mobility during hospitalization of older adults. *Journal of the American Geriatrics Society*, *57*(9), 1660–1665.
- Brown, C. J., Williams, B. R., Woodby, L. L., Davis, L. L., & Allman, R. M. (2007). Immobility, hospitalization and frailty. Barriers to mobility during hospitalization from the perspectives of older patients and their nurses and physicians. *Journal of Hospital Medicine*, *2*(5), 305–313.
- Brown, I., Renwick, R., & Raphael, D. (1995). Frailty: Constructing a common meaning, definition, and conceptual framework. *International Journal of Rehabilitation Research*, *18*(2), 93–102.
- Brown, M., Sinacore, D. R., Binder, E. F., & Kohrt, W. M. (2000). Physical and performance measures for the identification of mild to moderate frailty. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *55*(6), M350–M355.
- Brown, N. A., & Zenilman, M. E. (2010). The impact of frailty in the elderly on the outcome of surgery in the aged. *Advances in Surgery*, *44*(1), 229–249. doi:10.1016/j.yasu.2010.05.014
- Brown, S. J. (2004). The Braden Scale: A review of the research evidence. *Orthopedic Nursing*, *23*(1), 30–38.
- Bruce, M. L. (2001). Depression and disability in late life: Directions for future research. *American Journal of Geriatric Psychiatry*, *9*(2), 102–112.
- Buchman, A. S., Boyle, P. A., Wilson, R. S., Tang, Y., & Bennett, D. A. (2007). Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. *Psychosomatic Medicine*, *69*(5), 483–489.
- Buchman, A. S., Wilson, R. S., Bienias, L., & Bennett, D. A. (2009). Change in frailty and risk of death in older persons. *Experimental Aging Research*, *35*(1), 61–82.

- Buchner, D. M., & Wagner, E. H. (1992). Preventing frail health. *Clinics in Geriatric Medicine*, 8(1), 1–17.
- Budnitz, D. S., Shehab, N., Kegler, S. R., & Richards, C. L. (2007). Medication use leading to emergency department visits for adverse drug events in older adults. *Annals of Internal Medicine*, 147(11), 755–765.
- Bunk, J. M. (2007). Frailty: Meaningful concept or conceptual muddle? Master's thesis, gerontological studies. Miami University, Oxford, OH.
- Burke, G. L., Arnold, A. M., Bild, D. E., Cushman, M., Fried, L. P., Newman, A., . . . Robbins, J.; CHS Collaborative Research Group. (2001). Factors associated with healthy aging: The cardiovascular health study. *Journal of the American Geriatrics Society*, 49(3), 254–262.
- Burnside, I. (1990). The frail elderly: Those 85 and over. *Nursing Administration Quarterly*, 14(2), 37–41.
- Burnside, I., & Touhy, T. (2006). *Geriatric nursing: Growth of a specialty*. New York, NY: Springer Publishing Co.
- Butler, R. N. (1969). Age-ism: Another form of bigotry. *Gerontologist*, 9, 243–246.
- Byram, D. A. (2000). Leadership: A skill, not a role. *AACN Clinical Issues*, 11(3), 463–469.
- Cacciatore, R., Abete, P., Miati, M. L., Della Morte, D., D'Ambrosio, D., Gargiulo, G., . . . Rengo, F. (2005). Frailty predicts long term mortality in elderly subjects with chronic heart failure. *European Journal of Clinical Investigations*, 35, 723–730.
- Callen, B. L., Mahoney, J. E., Grieves, C. B., Wells, T. J., & Enloe, M. (2004). Frequency of hallway ambulation by hospitalized older adults on medical units of an academic hospital. *Geriatric Nursing*, 25(4), 212–217.
- Callen, B. L., Mahoney, J. E., Wells, T. J., Enloe, M., & Hughes, S. (2004). Admission and discharge mobility of frail hospitalized older adults. *Medsurg Nursing*, 13(3), 156–163.
- Campbell, A. J., & Buchner, D. M. (1997). Unstable disability and the fluctuations of frailty. *Age and Ageing*, 26, 315–318.
- Campbell, K. E. (2009). A new model to identify shared risk factors for pressure ulcers and frailty in older adults. *Rehabilitation Nursing*, 34(6), 242–247.

- Campbell, S. E., Seymour, D. G., & Primrose, W. R., for the ACMEplus Project. (2004). A systematic literature review of factors affecting outcome in older medical patients admitted to hospital. *Age & Ageing*, 33(2), 110–115.  
doi:10.1093/ageing/afh036
- Carlson, E. D., & Chamberlain, R. M. (2005). Allostatic load and health disparities: A theoretical orientation. *Research in Nursing & Health*, 28(4), 306–315.
- Carlson, J. E., Zocchi, K. A., Bettencourt, D. M., Gambrel, M. L., Freeman, J. L., Zhang, D., & Goodwin, J. S. (1998). Measuring frailty in the hospitalized elderly. Concept of functional homeostasis. *American Journal of Physical Medicine and Rehabilitation*, 77(3), 252–257.
- Carrière, I., Dupuy, A. M., Lacroux, A., Cristol, J. P., Delcourt, C.; Pathologies Oculaires Liées à l'Age Study Group. (2008). Biomarkers of inflammation and malnutrition associated with early death in healthy elderly people. *Journal of the American Geriatrics Society*, 56(5), 840–846.
- Castle, S. C., Uyemura, K. J., Rafi, A., Akande, O., & Makinodan, T. (2005). Comorbidity is a better predictor of impaired immunity than chronological age in older adults. *Journal of the American Geriatrics Society*, 53(9), 1565–1569.
- Cawthon, P. M., Marshall, L. M., Michael, Y., Dam, T. T., Ensrud, C. E., Barrett-Connor, E., & Orwoll, E. S. for the Osteoporotic Fractures in Men Research Group. (2007). Frailty in older men: Prevalence, progression, and relationship with mortality. *Journal of the American Geriatrics Society*, 55(8), 1216–1223.
- Cella, D., Lai, J. S., Chang, C. H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general united states population. *Cancer*, 94, 528–538.
- Centers for Disease Control and Prevention (CDC). (2012). *Chronic diseases and health promotion*. Atlanta, GA: CDC. Retrieved from <http://www.cdc.gov/chronicdisease/overview/index.htm>
- Centers for Medicare and Medicaid Services (CMS). (2006). *Medicare and Medicaid Programs: Programs of All-Inclusive Care for the Elderly (PACE)*. Program revisions. Federal Register, 42, Parts 460, 462, 473, and 476. Final Rule. Retrieved from [http://www.npaonline.org/website/download.asp?id=1783&title=PACE\\_Final\\_Rule\\_-\\_12/08/06](http://www.npaonline.org/website/download.asp?id=1783&title=PACE_Final_Rule_-_12/08/06)
- Centers for Medicare and Medicaid Services (CMS). (2012a). *National medicare readmission findings: Recent data and trends*. Office of Information Products and

Data Analytics Centers for Medicare and Medicare Services. Retrieved from <http://www.academyhealth.org/files/2012/sunday/brennan.pdf>

- Centers for Medicare and Medicaid Services (CMS). (2012b). *Readmission reduction program*. Retrieved from <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program.html>
- Cesari, M. (2011a). Role of gait speed in the assessment of older patients. *Journal of the American Medical Association*, *305*(1), 93–94.
- Cesari, M. (2011b). The multidimensionality of frailty: Many faces of one single dice. *Journal of Nutrition, Health, & Aging*, *15*(8), 663–664.
- Cesari, M., Kritchevsky, S. B., Newman, A. B., Simonsick, E. M., Harris, T. B., Penninx, B. W., . . . Pahor, M.; Health, Aging and Body Composition Study. (2009). Added value of physical performance measures in predicting adverse health-related events: results from the health, aging and body composition study. *Journal of the American Geriatrics Society*, *57*(2), 251–259.
- Cesari, M., Onder, G., Zamboni, V., Manini, T., Shorr, R.I., Russo, A., . . . Landi, F. (2008). Physical function and self-rated health status as predictors of mortality: Results from longitudinal analysis in the InCHIANTI study. *BMC Geriatrics*, *8*(34), 1–9.
- Cesari, M., Penninx, B. W., Newman A. B., Kritchevsky, S. B., Nicklas, B. J., Sutton-Tyrrell, K., . . . Pahor, M. (2003). Inflammatory markers and onset of cardiovascular events: Results from the health ABC study. *Circulation*, *108*(19), 2317–2322.
- Cesari, M., Penninx, B. W., Newman, A. B., Kritchevsky, S. B., Nicklas, B. J., Sutton-Tyrrell, K., . . . Pahor, M. (2003). Inflammatory markers and cardiovascular disease (the health, aging and body composition [Health ABC Study]). *American Journal of Cardiology*, *92*(5), 522–528.
- Cesari, M., Penninx, B. W., Pahor, M., Lauretani, F., Corsi, A.M., . . . Ferrucci, L. (2004). Inflammatory markers and physical performance in older persons: The InCHIANTI study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *59*(3), 242–248.
- Chalcraft, S. C. (2010). Assigning “frailty.” *Age and Ageing*, *39*(3), 405.
- Chang, E., Hancock, K., Hickman, L., Glasson, J., & Davidson, P. (2007). Outcomes of acutely ill older hospitalized patients following implementation of tailored models

- of care: A repeated measures (pre- and post-intervention) design. *International Journal of Nursing Studies*, 44(7), 1079–1092.
- Chang, S. S., Weiss, C. O., Xue, Q., & Fried, L. P. (2012). Association between inflammatory-related disease burden and frailty: Results from the women's health and aging studies (WHAS) I and II. *Archives of Gerontology and Geriatrics*, 54(1), 9–15. doi:10.1016/j.archger.2011.05.020
- Chang, S. S., Vaz Fragoso, C. A., Van Ness, P. H., Fried, L. P., & Tinetti, M. E. (2011). Association between combined interleukin-6 and c-reactive protein levels and pulmonary function in older women: results from the women's health and aging studies I and II. *Journal of the American Geriatrics Society*, 59(1), 113–119. doi:10.1111/j.1532-5415.2010.03203.x
- Chappell, N. L. (1991). Living arrangements and sources of caregiving. *Journal of Gerontology*, 46(1), S1–S8.
- Chater, K. (2002). Aging: A body of resistance. *Nursing and Health Sciences*, 4(3), 123–129.
- Chaves, P. H., Semba, R. D., Leng, S. X., Woodman, R. C., Ferrucci, L., Guralnik, J. M., & Fried, L. P. (2005). Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: The women's health and aging studies I and II. *Journals of Gerontology. Series A, Biologic Sciences and Medical Sciences*, 60(6), 729–735.
- Chaves, P. H., Ashar, B., Guralnik, J. M., & Fried, L. P. (2002). Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women: Should the criteria currently used to define anemia in older people be reevaluated? *Journal of the American Geriatrics Society*, 50(7), 1257–1264.
- Chen, C. C., Dai, Y. T., Yen, C. J., Huang, G. H., & Wang, C. (2010). Shared risk factors for distinct geriatric syndromes in older Taiwanese inpatients. *Nursing Research*, 59(5), 340–347.
- Chen, C. C., Yen, C. J., Dai, Y. T., Wang, C., & Huang, G. H. (2011). Prevalence of geriatric conditions: A hospital-wide survey of 455 geriatric inpatients in a tertiary medical center. *Archives of Gerontology and Geriatrics*, 53(1), 46–50.
- Chen, C. Y., Wu, S. C., Chen, L. J., & Lue, B. H. (2010). The prevalence of subjective frailty and factors associated with frailty in Taiwan. *Archives of Gerontology and Geriatrics*, 50(Suppl 1), S43–S47.

- Chiang, J. J., Eisenberger, N. I., Seeman, T. E., & Taylor, S. E. (2012). Negative and competitive social interactions are related to heightened proinflammatory cytokine activity. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(6), 1878–1882. doi:10.1073/pnas.1120972109
- Chin A Paw, M. J., de Groot, L. C., Gend, S. V., Schoterman, M. H., Schouten, E. G., Schroll, M., & Staveren, W. A. (2003). Inactivity and weight loss: Effective criteria to identify frailty. *Journal of Nutrition in Health and Aging*, *3*(1), 55–60.
- Cigolle, C. T., Ofstedal, M. B., Tian, Z., & Blaum, C. S. (2009). Comparing models of frailty: The health and retirement study. *Journal of the American Geriatrics Society*, *57*(5), 830–839.
- Clark, M. S., Bond, M. J., & Hecker, J. R. (2007). Environmental stress, psychological stress and allostatic load. *Psychology, Health & Medicine*, *12*(1), 18–30.
- Clark, R., Anderson, N. B., Clark, V. R., & Williams, D. R. (1999). Racism as a stressor for African Americans. *American Psychologist*, *54*(10), 805–816.
- Clark, V. R. (2001). The perilous effects of racism on blacks. *Ethnic Disparities*, *11*(4), 769–772.
- Clegg, A. (2011). The frailty syndrome. *Clinical Medicine*, *11*(1), 72–75.
- Clegg, A., Young, J., Iliffe, S., Rikkert, M.O., & Rockwood, K. (2013). Frailty in elderly people. *Lancet*, *381*(9868), 752–762. doi:10.1016/S0140-6736(12)62167-9
- Cleveland, J. C. (2010). Frailty, aging, and cardiac surgery outcomes: The stopwatch tells the story. *Journal of the American College of Cardiology*, *56*(20), 1677–1678.
- Cohen, H. J. (2000). Editorial: In search of the underlying mechanisms of frailty. *The Journals of Gerontology*, *55*(12), M706–M708.
- Cohen, H. J., Harris, T., & Pieper, C. F. (2003). Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. *American Journal of Medicine*, *114*(3), 180–187.
- Cohen, H. J., Pieper, C. F., Harris, T., Rao, K. M., & Currie, M. S. (1997). The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *52* (4), M201–M208.
- Cohen, R. R., Lagoo-Deenadayalan, S., Heflin, M. T., Sloane, R., Eisen, I., Thacker, J. M., & Whitson, H. E. (2012). Exploring predictors of complication in older

- surgical patients: a deficit accumulation index and the braden scale. *Journal of the American Geriatrics Society*, 60(9), 1609–1615. doi:10.1111/j.1532-5415.2012.04109.x.
- Cohen, S. (2004). Social relationships and health. *American Psychologist*, 59, 676–684.
- Cole, M., McCusker, J., Dendukuri, N., & Han, L. (2003). The prognostic significance of subsyndromal delirium in elderly medical inpatients. *Journal of the American Geriatrics Society*, 51(6), 754–760.
- Cole, M. G., Ciampi, A., Belzile, E., & Zhong, L. (2009). Persistent delirium in older hospital patients: A systematic review of frequency and prognosis. *Age & Ageing*, 38(1), 19–26. doi:10.1093/ageing/afn253
- Coles, L. S. (2004). Demography of human supercentenarians. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 59(6), 579–586.
- Collins, M., & Abeles, N. (1996). Subjective memory complaint in the able elderly. *Clinics in Gerontology*, 16, 29–54.
- Collins, S. (2007). *Associations between frailty and sex and frailty and race in hospitalized chronic heart failure patients: An exploratory study*. (Doctoral dissertation). Retrieved from ProQuest Information and Learning Company. Ann Arbor, MI. UMI Number: 3272807.
- Conroy, S. P., Stevens, T., Parker, S. G., & Gladman, J. R. (2010). A systematic review of comprehensive geriatric assessment to improve outcomes for frail older people being rapidly discharged from acute hospital: 'Interface geriatrics.' *Age & Ageing*, 40(4), 436–443. doi:10.1093/ageing/afr060
- Cooper, C., Dere, W., Evans, W., Kanis, J. A., Rizzoli, R., Sayer, A. A., . . . Reginster, J. Y. (2012). Frailty and sarcopenia: Definitions and outcome parameters. *Osteoporosis International*, 23(7), 1839–1848. doi:10.1007/s00198-012-1913-1
- Cornali, C., Franzoni, S., Frisoni, G. B., & Trabucchi, M. (2005). Anorexia as an independent predictor of mortality. *Journal of the American Geriatrics Society*, 53(2), 354–355.
- Corti, M. C., Guralnik, J. M., Salive, M. E., & Sorkin, J. D. (1994). Serum albumin level and physical disability as predictors of mortality in older persons. *Journal of the American Medical Association*, 272(13), 1036–1042.
- Counsell, S. R., Holder, C. M., Liebenauer, L. L., Palmer, R. M., Fortinsky, R. H., Kresevic, D. M., . . . Landefeld, C. S. (2000). Effects of a multicomponent

- intervention on functional outcomes and process of care in hospitalized older patients: A randomized controlled trial of acute care for elders (ACE) in a community hospital. *Journal of the American Geriatrics Society*, 48(12), 1572–1581.
- Covinsky, K. (2006). Aging, arthritis, and disability. *Arthritis and Rheumatology*, 55(2), 175–176.
- Covinsky, K. E., Covinsky, M. H., Palmer, R. M., & Sehgal, A. R. (2002). Serum albumin concentration and clinical assessments of nutritional status in hospitalized older people: Different sides of different coins? *Journal of the American Geriatrics Society*, 50(4), 631–637.
- Covinsky, K. E., Fortinsky, R. H., Palmer, R. M., Kresevic, D. M., & Landefeld, C. S. (1997). Relation between symptoms of depression and health status outcomes in acutely ill hospitalized older persons. *Annals of Internal Medicine*, 126(6), 417–425.
- Covinsky, K. E., Lindquist, K., Dunlop, D. D., & Yelin, E. (2009). Pain, functional limitations, and aging. *Journal of the American Geriatrics Society*, 57(9), 1556–1561.
- Covinsky, K. E., Lindquist, K., Dunlop, D. D., Gill, T. M., & Yelin, E. (2008). Effect of arthritis in middle age on older-age functioning. *Journal of the American Geriatrics Society*, 56(1), 23–28.
- Covinsky, K. E., Palmer, R. M., Fortinsky, R. H., Counsell, S. R., Stewart, A. L., Kresevic, D., . . . Landefeld, C. S. (2003). Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: Increased vulnerability with age. *Journal of the American Geriatrics Society*, 51(4), 451–458.
- Covinsky, K. E., Pierluissi, E., & Johnston, C.B. (2011). Hospitalization-associated disability: “She was probably able to ambulate, but I’m not sure.” *Journal of the American Geriatrics Society*, 306(16), 1782–1793.
- Covinsky, K. E., Yaffe, K., Lindquist, K., Cherkasova, E., Yelin, E., & Blazer, D. G. (2010). Depressive symptoms in middle age and the development of later-life functional limitations: The long-term effect of depressive symptoms. *Journal of the American Geriatrics Society*, 306(58), 551–556.
- Creditor, M. C. (1993). Hazards of hospitalization in the elderly. *Annals of Internal Medicine*, 118(3), 219–223.

- Crimmins, E. M., Kim, J. K., & Seeman, T. E. (2009). Poverty and biological risk: The earlier “aging” of the poor. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 64(2), 286–292.
- Danese A., Pariante C. M., Caspi A., Taylor A., & Poulton, R. (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences of the United States of America*, 104(4), 1319–1324.
- Dasgupta, M., Rolfson, D. B., Stolee, P., Borrie, M. J., & Speechley, M. (2009). Frailty is associated with postoperative complications in older adults with medical problems. *Archives of Gerontology and Geriatrics*, 48(1), 78–83.
- Davis, J. A., Robinson, R. L., Le, T. K., & Xie, J. (2011). Incidence and impact of pain conditions and comorbid illness. *Journal of Pain Research*, 4, 331–345.
- Dayhoff, N. E., Suhreinrich, J., Wigglesworth, J., Topp, R. & Moore, S. (1998). Balance and muscle strength as predictors of frailty among older adults. *Journal of Gerontological Nursing*, 24(7), 18–27.
- De Lepeleire, J., Iliffe, S., Mann, E., & Degryse, J. M. (2009). Frailty: An emerging concept for general practice. *British Journal of General Practice*, 59(562), e177–e182. doi:10.3399/bjgp09X420653
- De Martinis, M., Franceschi, C., Monti, D., & Ginaldi, L. (2005). Inflamm-aging and lifelong antigenic load as major determinants of ageing rate and longevity. *Federation of European Biochemical Studies*, 579(10), 2035–2039.
- De Martinis, M. D., Franceschi, C., Monti, D., & Ginaldi, L. (2006). Inflammation markers predicting frailty and mortality in the elderly. *Experimental and Molecular Pathology*, 80(3), 219–227.
- de Rooij, S. E., Schuurmans, M. J., van der Mast, R. C., & Levi, M. (2005). Clinical subtypes of delirium and their relevance for daily clinical practice: A systematic review. *International Journal of Geriatric Psychiatry*, 20(7), 609–615.
- de Saint-Hubert, M., Jamart, J., Boland, B., Swine, C., & Cornette, P. (2010). Comparison of three tools predicting functional decline after hospitalization of older patients. *Journal of the American Geriatrics Society*, 58(5), 1003–1005. doi:10.1111/j.1532-5415.2010.02839.x
- de Vries, H. F., Northington, G. M., & Bogner, H. R. (2012). Urinary incontinence (UI) and new psychological distress among community dwelling older adults. *Archives in Gerontology & Geriatrics*, 55(1), 49–54. doi:10.1016/j.archger.2011.04.012

- Deverts, D. J., Cohen, S., DiLillo, V. G., Lewis, C. E., Kiefe, C., Whooley, M., & Matthews, K. A. (2010). Depressive symptoms, race, and circulating c-reactive protein: The coronary artery risk development in young adults (CARDIA) study. *Psychosomatic Medicine*, *72*(8), 734–741. doi:10.1097/PSY. 0b013e3181ec4b98
- Don, B. R., & Kaysen, G. (2004). Serum albumin: Relationship to inflammation and nutrition. *Seminars in Dialysis*, *17*(6), 432–437.
- Donini, L. M., De Felice, M. R., Tagliaccica, A., De Bernardini, L., & Cannella, C. (2005). Comorbidity, frailty, and evolution of pressure ulcers in geriatrics. *Medical Science Monitor*, *11*(7), CR326–C336.
- Dong, X., Mendes de Leon, C., Artz, A., Tang, Y., Shah, R., & Evans, D. (2008). A population-based study of hemoglobin, race, and mortality in elderly persons. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *63*(8), 873–878.
- Dramé, M., Novella, J. L., Jolly, I., Laniece, D., Somme, D., Heitz, J. B., . . . Lang, P. O. (2011). Rapid cognitive decline, one-year institutional admission and one-year mortality: Analysis of the ability to predict and inter-tool agreement of four validated clinical frailty indexes in the SAFES cohort. *Journal of Nutrition, Health, & Aging*, *15*(8), 699–705.
- Dramé, M., Novella, J. L., Lang, P. O., Somme, D., Jovenin, N., Laniece, I., . . . Jolly, D. (2008). Derivation and validation of a mortality-risk index from a cohort of frail elderly patients hospitalised in medical wards via emergencies: The SAFES study. *European Journal of Epidemiology*, *23*, 783–791.
- DuBeau, C. E., Kuchel, G. A., Johnson, T. II, Palmer, M. H., & Wagg, A; Fourth International Consultation on Incontinence. (2010). Incontinence in the frail elderly: Report from the 4th international consultation on incontinence. *Neurourology Urodynamics*, *29*(1), 165–178. doi:10.1002/nau.20842
- Duke, C. (2005). The frail elderly community-based case management project. *Geriatric Nursing*, *26*(2), 122–127.
- Duivis, H. E., de Jonge, P., Penninx, B. W., Na, B. Y., Cohen, B. E., & Whooley, M. A. (2011). Depressive symptoms, health behaviors, and subsequent inflammation in patients with coronary heart disease: prospective findings from the heart and soul study. *American Journal of Psychiatry*, *168*(9), 913–920. doi:10.1176/appi.ajp.2011.10081163
- Dyer, C. B., Hyer, K., Feldt, K. S., Lindemann, D. A., Busby-Whitehead, J., Greenberg, S., Kennedy, R. D., & Flaherty, E. (2003). Frail older patient care by

interdisciplinary teams: A primer for generalists. *Gerontology & Geriatric Education*, 24(2), 51–62.

- Eeles, E. M., White, S. V., O'Mahony, S. M., Bayer, A. J., & Hubbard, R. E. (2012). The impact of frailty and delirium on mortality in older inpatients. *Age & Ageing*, 41(3), 412–416. doi:10. 1093/ageing/afs021
- Ekdahl, A. W., Andersson, L., & Friedrichsen, M. (2010). “They do what they think is the best for me”: Frail elderly patients’ preferences for participation in their care during hospitalization. *Patient Education and Counseling*, 80, 233–240.
- Ekman, I., Cleland, J. G., Swedberg, K., Charlesworth, A., Metra, M., & Poole-Wilson, P. A. (2005). Symptoms in patients with heart failure are prognostic predictors: insights from COMET. *Journal of Cardiac Failure*, 11(4), 288–292.
- Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, 19(4268), 129–136.
- Engel, G. L. (1981). Clinical application of the biopsychosocial model. *American Journal of Psychiatry*, 137(5), 535–544.
- Ensrud, K. E., Ewing, S. K., Cawthon, P. M., Fink, H. A., Taylor, B. C., Cauley, J. A., . . . Cummings, S. R.; Osteoporotic Fractures in Men Research Group. (2009). A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. *Journal of the American Geriatric Society*, 57(3), 492–498.
- Ensrud, K. E., Ewing, S. K., Taylor, B. C., Fink, H. A., Cawthon, P. M., Stone, K. L., . . . Cummings, S. R., for the Study of Osteoporotic Fractures Research Group. (2008). A comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Archives of Internal Medicine*, 168(4), 382–389.
- Ensrud, K. E., Ewing, S. K., Taylor, B. C., Fink, H. A., Stone, K. L., Cauley, J. A., . . . Cawthon, P. M., for the Study of Osteoporotic Fractures Group. (2007). Frailty and risk of falls, fracture, and mortality in older women: The study of osteoporotic fractures. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7), 744–751.
- Erlen, J. A. (2007). The frail elderly: A matter of caring. *Orthopedic Nursing*, 26(6), 379–382.
- Ershler, W. B. (2003). Biological interactions of aging and anemia: A focus on cytokines. *Journal of the American Geriatrics Society*, 51(Suppl), S18–S21.

- Ershler, W. B. (1993). Interleukin-6: A cytokine for gerontologists. *Journal of the American Geriatric Society*, 41(2), 176–181.
- Ershler, W. B., & Keller, E. T. (2000). Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annual Review of Medicine*, 51, 245–270.
- Farhat, J. S., Velanovich, V., Falvo, A. J., Horst, H. M., Swartz, A., Patton, J. H. Jr., & Rubinfeld, I. S. (2012). Are the frail destined to fail? Frailty index as predictor of surgical morbidity and mortality in the elderly. *Journal of Trauma and Acute Care Surgery*, 72(6), 1526–1530. doi:10.1097/TA.0b013e3182542fab
- Fedarko, N. S. (2011). The biology of aging and frailty. *Clinics in Geriatric Medicine*, 27(1), 27–37.
- Federal Interagency Forum on Aging Related Statistics. (2010). *Older Americans 2010: Key indicators of well-being*. Retrieved from [http://www.agingstats.gov/Agingstatsdotnet/Main\\_Site/default.aspx](http://www.agingstats.gov/Agingstatsdotnet/Main_Site/default.aspx)
- Fernandez-Bolaños, M., Otero, A., Zunzunegui, M. V., Beland, F., Alarcón, T., de Hoyos, C., & Castell, M. V. (2008). Sex differences in the prevalence of frailty in a population aged 75 and older in Spain. *Journal of the American Geriatric Society*, 56(12), 2370–2371.
- Ferrucci, L., Bandinelli, S., Benvenuti, E., Di Iorio, A., Macchi, C., Harris, T. B., & Guralnik, J. M. (2000). Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *Journal of the American Geriatric Society*, 48(12), 1618–1625.
- Ferrucci, L., Cavazzini, C., Corsi, A. M., Bartali, B., Russo, C. R., Laurentani, F., . . . Guralnik, J. M. (2002). Biomarkers of frailty in older persons. *Journal of Endocrinology Investigations*, 25, 10–15.
- Ferrucci, L., Guralnik, J. M., Studenski, S., Fried, L. P., Cutler, G. B., & Walston, J. D., for the Interventions on Frailty Working Group. (2004). Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, old persons: A consensus report. *Journal of the American Geriatrics Society*, 52(4), 625–634.
- Ferrucci, L., Mahallati, A., & Simonsick, E. M. (2006). Frailty and the foolishness of Eos. *Journals of Gerontology. Series A, Biological Science and Medical Science*, 61(3), 260–261.

- Ferrucci, L., Harris, T. B., Guralnik, J. M., Tracy, R. P., Corti, M. C., Cohen, H. J., . . . Havlik, R. J. (1999). Serum IL-6 level and the development of disability in older persons. *Journal of the American Geriatrics Society*, 47(6), 639–646.
- Field, A. (2009). *Discovering statistics using SPSS* (3rd ed.). Thousand Oaks, CA: Sage.
- Fillit, H., & Butler, R. N. (2009). The frailty identity crisis. *Journal of the American Geriatrics Society*, 57(2), 348–352.
- Finlayson, E. V., & Birkmeyer, J. D. (2001). Operative mortality with elective surgery in older adults. *Effective Clinical Practice*, 4(4), 172–177.
- Fitzpatrick, J. J., Salinas, T. K., O'Connor, L. J., Stier, L., Callahan, B., Smith, T., & White, M. T. (2004). Nursing care quality initiative for care of hospitalized elders and their families. *Journal of Nursing Care Quality*, 19(2), 156–161.
- Fitzpatrick, J. J., Stier, L., Eichorn, A., Dlugacz, Y. D., O'Connor, L. J., Salinas, T. K., . . . White, M. T. (2004). Hospitalized elders: Changes in functional and mental status. *Outcomes Management*, 8(1), 52–56.
- Ford, E. S., Loucks, E. B., & Berkman, L. F. (2006). Social integration and concentrations of c-reactive protein among US adults. *Annals of Epidemiology*, 16(2), 78–84.
- Ford, K., Sowers, M., Seeman, T. E., Greendale, G. A., Sternfeld, B., & Everson-Rose, S. A. (2010). Cognitive functioning is related to physical functioning in a longitudinal study of women at midlife. *Gerontology*, 56(3), 250–258.
- Forti, P., Rietti, E., Pisacane, N., Olivelli, V., Maltoni, B., & Ravaglia, G. (2012). A comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort. *Archives of Gerontology and Geriatrics*, 54(1), 16–20.
- Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., & De Benedictis, G. (2000). Inflamm-aging. An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Science*, 908, 244–254.
- Franceschi, C., Capri, M., Monti, D., Giunta, S., Olivieri, F., Sevini, F., . . . Salvioli, S. (2007). Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans. *Mechanisms of Aging and Development*, 128, 92–105.
- Fretwell, M. D. (1993). Prevention of functional decline in older hospitalized patients. *Rhode Island Medicine*, 76, 13–18.

- Fried, L. P., Herdman, S. J., Kuhn, K. E., Rubin, G., & Turano, K. (1991). Preclinical disability: Hypotheses about the bottom of the iceberg. *Journal of Aging & Health, 3*(2), 285–300.
- Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 59*(3), 255–563.
- Fried, L. P., Hadley, E. C., Walston, J. D., Newman, A. B., Guralnik, J. M., Studenski, S., . . . Ferrucci, L. (2005). From bedside to bench: Research agenda for frailty. *Science of Aging Knowledge Environment, 5*(31), pe24.  
doi:10.1126/sageke.2005.31.pe24
- Fried, T. R., & Mor, V. (1997). Frailty and hospitalization of long-term stay nursing home residents. *Journal of the American Geriatrics Society, 45*(3), 265–269.
- Fried, L. P., Storer, D. J., King, D. E., & Lodder, F. (1991). Diagnosis of illness presentation in the elderly. *Journal of the American Geriatrics Society, 39*(2), 117–123.
- Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., . . . McBurnie, M. A., for the Cardiovascular Health Study Collaborative Research Group. (2001). Frailty in older adults: Evidence for a phenotype. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 56*(3), M146–M156.
- Fried, L. P., & Walston, J. (1998). Frailty and failure to thrive. In W.R. Hazzard, J.P. Blass, W.H. Ettinger, jr., J.B. Halter, & J. Ouslander (Eds.). *Principles of geriatric medicine and gerontology* (4th ed., pp. 1387–1402). New York, NY: McGraw Hill, Inc.
- Fried, L.P., Young, Y., Rubin, G., Bandeen-Roche, K., & WHAS II Collaborative Research Group. (2001). Self-reported preclinical disability identifies older women with early declines in performance and early disease. *Journal of Clinical Epidemiology, 54*(9), 889–901.
- Fried, L. P., Xue, Q. L., Cappola, A. R., Ferrucci, L., Chaves, P., Varadhan, R., . . . Bandeen-Roche, K. (2009). Nonlinear multisystem physiological dysregulation associated with frailty in older women: Implications for etiology and treatment. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 64*(10), 1049–1057.

- Friedman, E. M., Karlamangla, A. S., Almeida, D. M., & Seeman, T. E. (2012). Social strain and cortisol regulation in midlife in the US. *Social Science in Medicine*, 74(4), 607–615. doi:10.1016/j.socscimed.2011.11.003
- Fries, J. F. (1980). Aging, natural death and the compression of morbidity. *New England Journal of Medicine*, 303(3), 130–135.
- Fries, J. F. (1988). Aging, illness, and health policy: Implications for the compression of morbidity. *Perspectives in Biological Medicine*, 31(3), 407–428.
- Fries, J. F. (2005). Frailty, heart disease, and stroke: The compression of morbidity paradigm. *American Journal of Preventive Medicine*, 29(5 Suppl. 1), 164–168.
- Fukuse, T., Satoda, N., Hijiya, K., & Fujinaga T. (2005). Importance of a comprehensive geriatric assessment in prediction of complications following thoracic surgery in elderly patients. *Chest*, 127(3), 886–891.
- Fugate Woods, N., LaCroix, A. Z., Gray, S. L., Aragaki, A., Cochrane, B. B., Brunner, R. L., . . . Newman, A. B. (2005). Frailty: Emergence and consequences in women aged 65 and older in the women's health initiative-observational study. *Journal of the American Geriatrics Society*, 53(8), 927–934.
- Fulmer, T., Mezey, M., Bottrell, M., Abraham, I., Sazant, J., Grossman, S., & Grisham, E. (2002). Nurses improving care for healthsystem elders (NICHE): Using outcomes and benchmarks for evidence-based practice. *Geriatric Nursing*, 23(2), 121–127.
- Fulton, M. M., & Allen, E. R. (2005). Polypharmacy in the elderly: A literature review. *Journal of the American Academy of Nurse Practitioners*, 17(4), 123–132.
- Fulop, T., Larbi, A., Witkowski, J. M., McElhaney, J., Loeb, M., Mitnitski, A., & Pawelec, G. (2010). Aging, frailty and age-related diseases. *Biogerontology*, 11(5), 547–563. doi:10.1007/s10522-010-9287-9292
- Galizia, G., Cacciatore, F., Testa, G., Della-Morte, D., Mazzella, F., Langellotto, A., . . . Abete, P. (2011). Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. *Aging Clinical and Experimental Research*, 23(2), 118–125.
- Gallagher, A. (2013). The good death. *Nursing Ethics*, 20(3), 243–244. doi:10.1177/0969733013482428.
- Gammack, J. K. (2004). Urinary incontinence in the frail elder. *Clinics in Geriatric Medicine*, 20(3), 453–466, vi.

- Gealey, S. G. (1997). Quantification of the term frail as applied to the elderly client. *Journal of the American Academy of Nurse Practitioners*, 9(11), 505–510.
- Genge, T. J. (2001). *Indicators of frailty in a community-dwelling seniors population*. (Doctoral dissertation). Retrieved from ProQuest Information and Learning Company, Ann Arbor, MI. UMI Number MQ69472).
- Geronimus, A. T. (2001). Understanding and eliminating racial inequalities in women's health in the United States: The role of the weathering conceptual framework. *Journal of American Medical Women's Association*, 56(4), 133–136.
- Geronimus, A. T., Hicken, M., Keene, D., & Bound, J. (2006). “Weathering” and age patterns of allostatic load scores among blacks and whites in the United States. *American Journal of Public Health*, 96(5), 826–833.
- Geronimus, A. T., Bound, J., Keene, D., & Hicken, M. (2007). Black-white differences in age trajectories of hypertension prevalence among adult women and men, 1999–2002. *Ethnic Disparities*, 17(1), 40–48.
- Gharacholou, M. S., Roger, V. L., Lennon, R. J., Rihal, C. S., Sloan, J. A., Spertus, J. A., & Singh, M. (2012). Comparison of frail patients versus nonfrail patients  $\geq 65$  years of age undergoing percutaneous coronary intervention. *American Journal of Cardiology*, 109(11), 1569–1575.
- Gill, J. M., & Szanton, S. (2011). Inflammation and traumatic stress: The society to cells resiliency model to support integrative interventions. *Journal of the American Psychiatric Nurses Association*, 17(6), 404–416.
- Gill, T. M. (2010). Assessment of function and disability in longitudinal studies. *Journal of the American Geriatrics Society*, 58(Suppl. 2), S308–S312.  
doi:10.1111/j.1532-5415.2010.02914.x
- Gill, T. M., Allore, H. G., Gahbauer, E. A., & Murphy, T. E. (2010). Change in disability after hospitalization or restricted activity in older people. *Journal of the American Medical Association*, 304(17), 1919–1928.
- Gill, T. M., Gahbauer, E. A., Allore, H. G., & Han, L. (2006). Transitions between frailty states among community-living older persons. *Archives of Internal Medicine*, 166(4), 418–423.
- Gill, T. M., Gahbauer, E. A., Han, L., & Allore, H. G. (2008). Functional trajectories in older persons admitted to a nursing home with disability after an acute hospitalization. *Journal of the American Geriatrics Society*, 57(2), 195–201.

- Gill, T. M., Gahbauer, E. A., Han, L., & Allore, H. G. (2009). Factors associated with recovery of prehospital function among older persons admitted to a nursing home with disability after an acute hospitalization. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *64*(12), 1296–1303.
- Gill, T. M., Gahbauer, E. A., Han, L., & Allore, H. G. (2010). Trajectories of disability in the last year of life. *New England Journal of Medicine*, *362*(13), 1173–1180.
- Gill, T. M., Gahbauer, E. A., Han, L., & Allore, H. G. (2011). The relationship between intervening hospitalizations and transitions between frailty states. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *66*(11), 1238–1243. doi:10.1093/gerona/qlr142
- Gillick, M. R. (1989). Long term care options for the frail elderly. *Journal of the American Geriatrics Society*, *37*(12), 1198–1203.
- Gilliss, C. L. (2011). Comment on: Building academic geriatric nursing capacity: Results after the first 10 years and implications for the future. *Nursing Outlook*, *59*(4), 205–206. doi:10.1016/j.outlook.2011.05.013
- Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews*, *5*(3), 243–251.
- Glei, D. A., Goldman, N., Chuang, Y. L., & Weinstein, M. (2007). Do chronic stressors lead to physiological dysregulation? Testing the theory of allostatic load. *Psychosomatic Medicine*, *69*(8), 769–776.
- Gnjidic, D., Hilmer, S. N., Blyth, F. M., Naganathan, V., Waite, L., Seibel M. J., . . . Le Couteur, D. G. (2012). Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *Journal of Clinical Epidemiology*, *65*(9), 989–995.
- Gobbens, R. J., Luijkx, K. G., Wijnen-Sponselee, W., & Schols, J. M. (2010a). In search of an integral conceptual definition of frailty: Opinions of experts. *Journal of the American Medical Directors Association*, *11*(5), 338–343.
- Gobbens, R. J., Luijkx, K. G., Wijnen-Sponselee, W., & Schols, J. M. (2010b). The Tilburg Frailty Indicator: Psychometric properties. *Journal of the American Medical Directors Association*, *11*(5), 344–355.
- Gobbens, R. J., Luijkx, K. G., Wijnen-Sponselee, W., & Schols, J. M. (2010c). Toward a conceptual definition of frail community dwelling older people. *Nursing Outlook*, *58*(2), 76–86.

- Gobbens, R. J., van Assen, M. A., Luijkx, K. G., & Schols, J. M. (2011). Testing an integral conceptual model of frailty. *Journal of Advanced Nursing*, Article published online: 7 DEC 2011. doi:10.1111/j.1365-2648.2011.05896.x
- Gobbens, R. J., van Assen, M. A., Luijkx, K. G., & Wijnen-Sponselee, M. T. (2010). Determinants of frailty. *Journal of the American Medical Directors Association*, 11(5), 356–364.
- Goldberg, R. M., Mabee, J., Chan, L., & Wong, S. (1996). Drug-drug and drug-disease interactions in the ED: Analysis of a high-risk population. *American Journal of Emergency Medicine*, 14(5), 447–450.
- Goldman, N., Gleib, D. A., Seplaki, C., Liu, I. W., & Weinstein, M. (2005). Perceived stress and physiological dysregulation in older adults. *Stress*, 8(2), 95–105.
- Goodwin, J. S., Howrey, B., Zhang, D. D., & Kuo, Y. F. (2011). Risk of continued institutionalization after hospitalization in older adults. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 66(12), 1321–1327.
- Gouin, J. P., Hantsoo, L., & Kiecolt-Glaser, J. K. (2008). Immune dysregulation and chronic stress among older adults: A review. *Neuroimmunomodulation*, 15(4–6), 251–259.
- Graf, C. (2006). Functional decline in hospitalized older adults. *American Journal of Nursing*, 106(1), 58–67.
- Graham, J. E., Snih, S. A., Berges, I. M., Ray, L. A., Markides, K. S., & Ottenbacher, K. J. (2009). Frailty and 10-year mortality in community-living Mexican American older adults. *Gerontology*, 55(6), 644–651. doi:10.1159/000235653
- Gray, R. (1998). Constructions of frailty in a senior housing facility. *Dissertation Abstracts International*, Department of Speech Communication, University of Washington.
- Gregory, P. C., Szanton, S. L., Xue, Q. L., Tian, J., Thorpe, R. J., & Fried, L. P. (2011). Education predicts incidence of preclinical mobility disability in initially high-functioning older women. The Women's Health and Aging Study II. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 66(5), 577–581. doi:10.1093/gerona/qlr023
- Grenier, A. M. (2002). Diverse older women: Narratives negotiating frailty. *Dissertation Abstracts International*, School of Social Work, McGill University, Montreal, Canada.

- Grenier, A. M., & Hanley, J. (2007). Older women and “frailty.” *Current Sociology*, 55(2), 211–228. doi:10.1177/0011392107073303
- Grossman, S.C., & Valiga, T.M. (2013). *The new leadership challenge. Creating the future of nursing*. (4th ed.). Philadelphia, PA: F.A. Davis Company.
- Gruenewald, T. L., Seeman, T. E., Karlamangla, A. S., & Sarkisian, C. A. (2009). Allostatic load and frailty in older adults. *Journal of the American Geriatrics Society*, 57(9), 1525–1531.
- Gruenewald, T. L., Seeman, T. E., Ryff, C. D., Karlamangla, A. S., & Singer, B. H. (2006). Combinations of biomarkers predictive of later life mortality. *Proceeds of the National Academy of Sciences USA*, 103(38), 1458–1463.
- Guralnik, J. M., & Ferrucci, L. (2003). Assessing the building blocks of function: Utilizing measures of functional limitation. *American Journal of Preventive Medicine*, 25(3, Suppl. 2), 112–121.
- Guralnik, J. M., Ferrucci, L., Pieper, C. F., Leveille, S. G., Markides, K. S., Ostir, G. V., . . . Wallace, R. B. (2000). Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *Journals of Gerontology. Series A, Biological Sciences & Medical Sciences*, 55(4), M221–M223.
- Guralnik, J. M., Land, K. C., Blazer, D., Fillenbaum, G. G., & Branch, L. G. (1993). Educational status and active life expectancy among older blacks and whites. *New England Journal of Medicine*, 329(2), 110–116.
- Gurung, R. A., Taylor, S. E., & Seeman, T. E. (2003). Accounting for changes in social support among married older adults: Insights from the MacArthur Studies of Successful Aging. *Psychology and Aging*, 18(3), 487–496.
- Hackstaff, L. (2009). Factors associated with frailty in chronically ill older adults. *Social Work in Health Care*, 48, 798–811.
- Hadley, E. C., Ory, M. G., Suzman, R., Weindruch, R., & Fried, L. (Eds.). (1993). Physical frailty: A treatable cause of dependence in old age. Forward. *Journals of Gerontology*, 48(8), vii–viii.
- Hajjar, E. R., Cafiero, A. C., & Hanlon, J. T. (2007). Polypharmacy in elderly patients. *The American Journal of Geriatric Pharmacotherapy*, 5(4), 345–351. doi:10.1016/j.amjopharm.2007.12.002

- Hall, M. G., DeFrances, C. J., Williams, S. N., Golosinskiy, A., & Schwartzman, A. (2010). *National Hospital Discharge Survey: 2007 Summary*. Division of Health Care Statistics. National Health Statistics Reports. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Number 29, October 26, 2010. Retrieved from <http://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf>
- Hamerman, D. (1999). Towards an understanding of frailty. *Annals of Internal Medicine*, 130(11), 945–950.
- Hancock, D., Helfers, M. J., Cowen, K., Letvak, S., Barba, B. E., Herrick, C., . . . Bannon, M. (2006). Integration of gerontology content in nongeriatric undergraduate nursing courses. *Geriatric Nursing*, 27(2), 103–111.
- Hardy, S. E., Perera, S., Roumani, Y. F., Chandler, J. M., & Studenski, S. A. (2007). Improvement in usual gait speed predicts better survival in older adults. *Journal of the American Geriatrics Society*, 55(11), 1727–1734.
- Hardy, S. E., & Studenski, S. A. (2008). Fatigue and function over 3 years among older adults. *Journals of Gerontology. Series A, Biological Sciences & Medical Sciences*, 63(12), 1389–1392.
- Hardy, S. E., & Studenski, S. A. (2010). Qualities of fatigue and associated chronic conditions among older adults. *Journal of Pain and Symptom Management*, 39(6), 1033–1042.
- Haren, M. T., Malmstrom, T. K., Miller, D. K., Patrick, P., Perry, H. M., Herning, M. M., . . . Morley, J. E. (2010). Higher c-reactive protein and soluble tumor necrosis factor receptor levels are associated with poor physical function and disability: A cross-sectional analysis of a cohort of late middle-aged African Americans. *The Journals of Gerontology. Series A, Biological Science and Medical Sciences*, 65(3), 274–281. doi:10.1093/gerona/qlp148
- Harimurti, K., & Setiati, S. (2007). C-reactive protein levels and decrease of albumin levels in hospitalized elderly patients with community-acquired pneumonia. *Acta Medica Indonesiana*, 39(1), 13–18.
- Harper, C. M., & Lyles, Y. M. (1988). *Journal of the American Geriatrics Society*, 36(11), 1047–1054.
- Harvey, I. S., & Silverman, M. (2007). The role of spirituality in the self-management of chronic illness among older African and whites. *Journal of Cross Cultural Gerontology*, 22, 205–220.

- Hastings, S. N., Purser, J. L., Johnson, K. S., Sloane, R. J., & Whitson, H. E. (2008). Frailty predicts some but not all adverse outcomes in older adults discharged from the emergency department. *Journal of the American Geriatrics Society*, *56*(9), 1651–1657.
- Hazzard, W. R. (2001). Depressed albumin and high-density lipoprotein cholesterol: Signposts along the final common pathway of frailty. *Journal of the American Geriatric Society*, *49*(9), 1253–1254.
- Healthy People 2020. (2013). *Older adults objectives*. Updated April 24, 2013. Retrieved from <http://healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=31>
- Heath, H., & Phair, L. (2009). The concept of frailty and its significance in the consequences of care or neglect for older people: An analysis. *International Journal of Older People Nursing*, *4*(2), 120–131. doi:10.1111/j.1748-3743.2009.00165.x
- Heppenstall, C. P., Hanger, H. C., & Wilkinson, T. J. (2009). Predictors of discharge stability in the first year following hospital admission for a frail elderly population. *Internal Medicine Journal*, *39*(3), 170–173.
- Heppenstall, C. P., Wilkinson, T. J., Hanger, H. C., & Keeling, S. (2009). Frailty: Dominos or deliberation? *New Zealand Medical Journal*, *122*(1299), 42–53.
- Herrmann, F. R., Safran, C., Levkoff, S. E., & Minaker, K. L. (1992). Serum albumin level on admission as a predictor of death, length of stay, and readmission. *Archives of Internal Medicine*, *152*(1), 125–130.
- Hetzel, L., & Smith, A. (2001). *The 65 years and older population. Census 2000 brief*. U.S. Census Bureau, October, 2001. Retrieved from <https://www.census.gov/prod/2001pubs/c2kbr01-10.pdf>
- Heuberger, R. A. (2011). The frailty syndrome: A comprehensive review. *Journal of Nutrition in Gerontology and Geriatrics*, *30*(4), 315–368. doi:10.1080/21551197.2011.623931
- Higby, H. R. (2001). *The characterization of frailty in the elderly: Perceptions of older adults and their primary caregivers*. (Doctoral dissertation). University of California, San Francisco. ISBN: 978-0-493-47671-1
- Hilmer, S. N., Mager, D. E., Simonsick, E. M., Ling, S. M., Windham, B. G., Harris, T. B., . . . Abernethy, D. R.; Health ABC Study. (2009). Drug burden index score

- and functional decline in older people. *American Journal of Medicine*, 122(12), 1142–1149. doi:10.1016/j.amjmed.2009.02.021
- Hilmer, S. N., Perera, V., Mitchell, S., Murnion, B. P., Dent, J., Bajorek, B., . . . Rolfson, D. B. (2009). The assessment of frailty in older people in acute care. *Australasian Journal of Ageing*, 28(4), 182–188. doi:10.1111/j.1741-6612.2009.00367.x
- Hirsch, C., Anderson, M. L., Newman, A., Kop, W., Jackson, S., Gottdiener, J., . . . Fried, L. P., for the Cardiovascular Health Study Research Group. (2006). The association of race with frailty: The cardiovascular health study. *Annals of Epidemiology*, 16(7), 545–553.
- Hitcho, E. B., Krauss, M. J., Birge, S., Dunagan, W. C., Fischer, I., Johnson, S., . . . Fraser, V. J. (2004). Characteristics and circumstances of falls in a hospital setting: A prospective analysis. *Journal of General Internal Medicine*, 19(7), 732–739. doi:10.1111/j.1525-1497.2004.30387.x
- Ho, Y. Y., Matteini, A. M., Beamer, B., Fried, L., Xue, Q. L., Arking, D. E., Chakravarti, A., Fallin, M. D., & Walston, J. (2011). Exploring biologically relevant pathways in frailty. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 66(9), 975–979.
- Hogan, D. B. (2006). Models, definitions, and criteria for frailty. In P. M. Conn (Ed.), *Handbook of Models for Human Aging* (pp. 619–629). Burlington, MA: Elsevier Academic Press.
- Hogan, D. B., MacKnight, C., & Bergman, H. (2003). Models, definitions, and criteria of frailty. *Ageing Clinical and Experimental Research*, 15(3 Suppl), 1–29.
- Hoogerduijn, J. G., Schuurmans, M. J., Duijnste, M. S., de Rooij, S. E., & Grypdonck, M. F. (2007). A systematic review of predictors and screening instruments to identify older hospitalized patients at risk for functional decline. *Journal of Clinical Nursing*, 16(1), 46–57.
- Hoogerduijn, J. G., Schuurmans, M. J., Korevaar, J. C., Buurman, B. M., & de Rooij, S. E. (2010). Identification of older hospitalised patients at risk for functional decline, a study to compare the predictive values of three screening instruments. *Journal of Clinical Nursing*, 19(9–10), 1219–1225. doi:10.1111/j.1365-2702.2009.03035.x
- Horowitz, A. (1985). Family caregiving to the frail elderly. *Annual Review of Gerontology & Geriatrics*, 5, 194–246.

- Horvath, M. M., Winfield, S., Evans, S., Slopek, S., Shang, H., & Ferranti, J. (2011). The DEDUCE guided query tool: Providing simplified access to clinical data for research and quality improvement. *Journal of Biomedical Informatics*, *44*, 266–276. doi:10.1016/j.jbi.2010.11.008
- Hubbard, R. E., Lang, I. A., Llewellyn, D. J., & Rockwood, K. (2010). Frailty, body mass index, and abdominal obesity in older people. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *65*(4), 377–381.
- Hubbard, R. E., O'Mahony, S., & Woodhouse, K. W. (2008). Characterizing frailty in the clinical setting: A comparison of different approaches. *Age and Aging*, *38*(1), 115–119.
- Hubbard, R. E., & Rockwood, K. (2011). Frailty in older women. *Maturitas*, *69*(3), 203–207. doi:10.1016/j.maturitas.2011.04.006
- Hubbard, R. E., Searle, S. D., Mitnitski, A., & Rockwood, K. (2009). Effect of smoking on the accumulation of deficits, frailty and survival in older adults: A secondary analysis from the Canadian study of health and aging. *Journal of Nutrition in Health & Aging*, *13*(5), 468–472.
- Hubbard, R. E., & Woodhouse, K. W. (2010). Frailty, inflammation and the elderly. *Biogerontology*, *11*(5), 635–641. doi:10.1007/s10522-010-9292-5
- Huck, S. W. (2008). *Reading statistics and research* (5th ed.). Boston, MA: Pearson.
- Ingold, B. B., Yersin, B., Wietlisbach, V., Burckhardt, P., Bumand, B., & Büla, C. J. (2000). Characteristics associated with inappropriate hospital use in elderly patients admitted to a general internal medicine service. *Aging (Milan, Italy)*, *12*(6), 430-438.
- Inouye, S.K, Bogardus, S.T., Jr., Baker, D.I., Leo-Summers, L., & Cooney, L.M. (2000). The hospital elder life program: A model of care to prevent cognitive and functional decline in older hospitalized patients. *Journal of the American Geriatrics Society*, *48*(12), 1697-1706.
- Inouye, S. K., & Charpentier, P. A. (1996). Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *Journal of the American Medical Association*, *275*(11), 852–857.
- Inouye, S. K., Schlesinger, M. J., & Lydon, T. J. (1999). Delirium: A symptom of how hospital care is failing older persons and a window to improve quality of hospital care. *American Journal of Medicine*, *106*(5), 565–573.

- Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *Journal of the American Geriatrics Society*, *55*(5), 780–791.
- Institute of Medicine (IOM). (1991). *Extending life, enhancing life: A national research agenda on aging*. Washington, DC: National Academy Press.
- Institute of Medicine (IOM). (2001). *Crossing the quality chasm: A new health system for the 21st century*. Washington, DC: The National Academies Press.
- Institute of Medicine (IOM). (2008). *Retooling for an aging America: Building the health care workforce*. Washington, DC: The National Academies Press.
- Ishihara-Paul, L., Wainwright, N. W., Khaw, K. T., Luben, R. N., Welch, A. A., Day, N. E., . . . Surtees, P. G. (2008). Prospective association between emotional health and clinical evidence of Parkinson's disease. *European Journal of Neurology*, *15*(11), 1148–1154. doi:10.1111/j.1468-1331.2008.02299.x
- Iwata, M., Kuzuya, M., Kitagawa, Y., & Iguchi, A. (2006). Prognostic value of serum albumin combined with serum c-reactive protein levels in older hospitalized patients: Continuing importance of serum albumin. *Aging Clinical and Experimental Research*, *18*(4), 307–311.
- Izaks, G. J., & Westendorp, R. G. (2003). Ill or just old? Towards a conceptual framework of the relation between aging and disease. *BMC Geriatrics*, *3*, 7. doi:10.1186/1471-2318-3-7
- Izaks, G. J., Westendorp, R. G., & Knook, D. L. (1999). The definition of anemia in older persons. *Journal of the American Medical Association*, *281*(18), 1714–1717. doi:10.1001/jama.281.18.1714
- Jaremka, L. M., Fagundes, C. P., Glaser, R., Bennett, J. M., Malarkey, W. B., & Kiecolt-Glaser, J. K. (2013). Loneliness predicts pain, depression, and fatigue: Understanding the role of immune dysregulation. *Psychoneuroendocrinology*, *38*(8), 1310–1317. doi:10.1016/j.psyneuen.2012.11.016
- Jaremka, L. M., Fagundes, C. P., Peng, J., Bennett, J. M., Glaser, R., Malarkey, W. B., & Kiecolt-Glaser, J. K. (2013). Loneliness promotes inflammation during acute stress. *Psychological Sciences*, Apr 29. [Epub ahead of print]
- James, S. A., Keenan, N. L., Strogatz, D. S., Browning, S. R., & Garrett, J. M. (1992). Socioeconomic status, John Henryism, and blood pressure in black adults. The Pitt County study. *American Journal of Epidemiology*, *135*(1), 59–67.

- Jarrett, P. G., Rockwood, K., Carver, D., Stolee, P., & Cosway, S. (1995). Illness presentation in elderly patients. *Archives of Internal Medicine*, *155*(10), 1060–1064.
- Jarosz, P. A., & Bellar, A. (2009). Sarcopenic obesity: An emerging cause of frailty in older adults. *Geriatric Nursing*, *30*(1), 64–70.
- Jayadevappa, R., Bloom, B. S., Raziano, D. B., & Lavizzo-Mourey, R. (2003). Dissemination and characteristics of acute care for elders (ACE) units in the United States. *International Journal of Technology Assessment in Health Care*, *19*(1), 220–227.
- Jeejeebhoy, K. N. (2012). Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: Overlap of clinical features. *Current Opinion in Clinical Nutrition and Metabolic Care*, *15*(3), 213–219. doi:10.1097/MCO.0b013e328352694f
- Jencks, S. F., Williams, M. V., & Coleman, E. A. (2009). Rehospitalizations among patients in the Medicare fee-for-service program. *New England Journal of Nursing*, *360*(14), 1418–1428.
- Jett, K. F. (1994). *Elderly rural African-American women alone: Strategies, choices and frailty*. Dissertation, University of Florida, Gainesville, FL.
- Jeune, B. (2002). Living longer—but better? *Aging Clinical and Experimental Research*, *14*(2), 72–93.
- Jones, D., Song, X., Mitnitski, A., & Rockwood, K. (2005). Evaluation of a frailty index based on a comprehensive geriatric assessment in a population based study of elderly Canadians. *Aging Clinical and Experimental Research*, *17*(6), 465–471.
- Jung, Y., Gruenewald, T. L., Seeman, T. E., & Sarkisian, C.A. (2010). Productive activities and development of frailty in older adults. *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *65B*(2), 256–261. doi:10.1093/geronb/gbp105
- Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, *35*(1), 2–16.
- Kaiser, M. J., Bandinelli, S., & Lunenfeld, B. (2009). The nutritional pattern of frailty. Proceedings from the 5th Italian congress of endocrinology of aging, Parma, Italy, 27–28 March 2009. *Aging Male*, *12*(4), 87–94. doi:10.3109/13685530903296706

- Kaiser, M., Bandinelli, S., & Lunenfeld, B. (2010). Frailty and the role of nutrition in older people. A review of the current literature. *Acta Bio-medica*, *81*(Suppl. 1), 37–45.
- Kamaruzzaman, S., Ploubidis, G. B., Fletcher, A., & Ebrahim, S. (2010). A reliable measure of frailty for a community dwelling older population. *Health and Quality of Life Outcomes*, *8*, 123. doi:10.1186/1477-7525-8-123
- Kanapuru, B., & Ershler, W. B. (2009). Inflammation, coagulation, and the pathway to frailty. *American Journal of Medicine*, *122*(7), 605–613. doi:10.1001/j.amjmed.2009.01.030
- Kane, R. L., Talley, K. M. C., Shamliyan, T., & Pacala, J. T. (Eds.). (2011). Common syndromes in older adults related to primary and secondary prevention. Rockville, MD: Agency for Healthcare Research and Quality (US); July 2011. Report No.: 11-05157-EF-1. Copyright notice: <http://www.ncbi.nlm.nih.gov/books/about/copyright/>
- Karlamangla, A. S., Singer, B. H., McEwen, B. S., Rowe, J. W., & Seeman, T. E. (2002). Allostatic load as a predictor of functional decline: MacArthur Studies of Successful Aging. *Journal of Clinical Epidemiology*, *55*(7), 696–710.
- Karunanathan, S., Wolfson, C., Bergman, H., Béland, F., & Hogan, D. B. (2009). A multidisciplinary systematic literature review on frailty: Overview of the methodology used by the Canadian initiative on frailty and aging. *BMC Medical Research Methodology*, *12*(9), 68. doi:10.1186/1471-2288-9-68
- Katz, S., Branch, L. G., Branson, M. H., Papsidero, J. A., Beck, J. C., & Greer, D. S. (1983). Active life expectancy. *New England Journal of Medicine*, *309*(20), 1218–1224.
- Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *Journal of the American Medical Association*, *21*(185), 914–919.
- Kaufman, S. R. (1994). The social construction of frailty: An anthropological perspective. *Journal of Aging Studies*, *8*(1), 45–58.
- Kautter, J., Ingber, M., & Pope, G. C. (2008–2009). Medicare risk adjustment for the frail elderly. *Health Care Financing Review*, *30*(20), 83–93.
- Kehl, K. A. (2006). Moving toward peace: An analysis of the concept of a good death. *American Journal of Hospital Palliative Care*, *23*(4), 277–286.

- Keller, H. H. (1993). Use of serum albumin for diagnosing nutritional status in the elderly—is it worth it? *Clinical Biochemistry*, 26(6), 435–437.
- Keller, B. K., Morton, J. L., Thomas, V. S., & Potter, J. F. (1999). The effect of visual and hearing impairments on functional status. *Journal of the American Geriatrics Society*, 47(11), 1319–1325.
- Khan, B. A., Zawahiri, M., Campbell, N. L., Fox, G. C., Weinstein, E. J., Nazir, A., . . . Boustani, M. A. (2012). Delirium in hospitalized patients: Implications of current evidence on clinical practice and future avenues for research—A systematic evidence review. *Journal of Hospital Medicine*, 7(7), 580–589. doi:10.1002/jhm.1949
- Kiecolt-Glaser, J. K., Loving, T. J., Stowell, J. R., Malarkey, W. B., Lemeshow, S., Dickinson, S. L., & Glaser, R. (2005). Hostile marital interactions, proinflammatory cytokine production, and wound healing. *Archives of General Psychiatry*, 62(12), 1377–1384.
- Kiecolt-Glaser, J. K., Preacher, K. J., MacCallum, R. C., Atkinson, C., Malarkey, W. B., & Glaser, R. (2003). Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Science*, 100(15), 9090–9095.
- Kiely, D. K., Cupples, L. A., & Lipsitz, L. A. (2009). Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. *Journal of the American Geriatrics Society*, 57(9), 1532–1539.
- Kinney, J. M. (2004). Nutritional frailty, sarcopenia and falls in the elderly. *Current Opinion in Clinical Nutrition and Metabolic Care*, 7(1), 15–20.
- Kiss, E., & Szodoray, P. (2010). Novel therapeutic approaches in systemic lupus erythematosus. *Frontiers in Bioscience (Scholar Edition)*, 2, 221–228.
- Klein, B. E., Klein, R., Knudtson, M. D., & Lee, K. E. (2003). Relationship of measures of frailty to visual function: The beaver dam eye study. *Transactions of the American Ophthalmological Society*, 101, 191–196.
- Klein, B. E., Klein R., Knudston, M. D., & Lee, K. E. (2005). Frailty, morbidity and survival. *Archives of Gerontology and Geriatrics*, 41(2), 141–149.
- Klein, B. E., Moss, S. E., Klein, R., Lee, K. E., & Cruickshanks, K. J. (2003). Associations of visual function with physical outcomes and limitations five years later in an older population: The Beaver Dam Eye Study. *Ophthalmology*, 110, 644–650. doi:10.1016/S0161-6420(02)01935-8

- Klijs, B., Nusselder, W. J., Looman, C. W., & Mackenbach, J. P. (2011). Contribution of chronic disease to the burden of disability. *PLoS One*, *6*(9), e25325. doi:10.1371/journal.pone.0025325
- Knudtson, M. D., Klein, B. E., & Klein, R. (2009). Biomarkers of aging and falling: The Beaver Dam Eye Study. *Archive of Gerontology and Geriatrics*, *49*(1), 22–26.
- Ko, F. C. (2011). The clinical care of frail, older adults. *Clinics in Geriatric Medicine*, *27*(1), 89–100. doi:10.1016/j.cger.2010.08.007
- Koelewijn, C. L., Schwartz, M. P., Samsom, M., & Oldenburg, B. (2008). C-reactive protein levels during a relapse of crohn's disease are associated with the clinical course of the disease. *World Journal of Gastroenterology*, *14*(1), 85–89.
- Koenig, H. G., George, L. K., & Titus, P. (2004). Religion, spirituality, and health in medically hospitalized older patients. *Journal of the American Geriatrics Society*, *52*(4), 554–562.
- Koster, A., Bosma, H., Penninx, B. W., Newman, A. B., Harris, T. B., van Eijk, J. T., . . . Kritchevsky, S. B., for the Health ABC Study. (2006). Association of inflammatory markers with socioeconomic status. *Journal of Gerontology. Series A. Biological Sciences and Medical Sciences*, *61*(3), 284–290.
- Kowlowitz, V., Davenport, C. S., & Palmer, M. H. (2009). Development and dissemination of Web-based clinical simulations for continuing geriatric nursing education. *Journal of Gerontological Nursing*, *35*(4), 37–43.
- Krabbe, K. S., Pederson, M., & Bruunsgaard, H. (2004). Inflammatory mediators in the elderly. *Experimental Gerontology*, *39*(5), 687–699.
- Kris, A. E., & Dodd, M. J. (2004). Symptom experience of adult hospitalized medical-surgical patients. *Journal of Pain and Symptom Management*, *28*, 451–459.
- Kristjansson, S. R., Nesbakken, A., Jordhoy, M. S., Skovlund, E., Audisio, R. A., Johannessen, . . . Wyller, T. B. (2010). Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: A prospective observational cohort study. *Critical Reviews in Oncology/Hematology*, *76*(3), 208–217.
- Kuchel, G. A. (2009). Frailty, allostatic load, and the future of predictive gerontology. *Journal of the American Geriatrics Society*, *57*(9), 1704–1706. doi:10.1111/j.1532-5415.2009.02406.x

- Kuh, D. (2007). A life course approach to healthy aging, frailty, and capability. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7), 717–721.
- Kuller, L. H., Tracy, R., Bellosso, W., De Wit, S., Drummond, F., Lane, H. C., . . . Neaton, J. D.; INSIGHT SMART Study Group. (2008). Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Medicine*, 5(10), e203. doi:10.1371/journal.pmed.0050203
- Kulminski, A., Ukraintseva, S. V., Akushevich, I., Arbeev, K. G., Land, K., & Yashin, A. I. (2007). Accelerated accumulation of health deficits as a characteristic of aging. *Experimental Gerontology*, 42(10), 963–970.
- Kumari, M., Badrick, E., Chandola, T., Adam, E. K., Stafford, M., Marmot, M.G., . . . Kivimaki, M. (2009). Cortisol secretion and fatigue: Associations in a community based cohort. *Psychoneuroendocrinology*, 34(10), 1476–1485.
- Lachs, M. S., Feinstein, A. R., Cooney, L. M., Drickamer, M. A., Marottoli, R. A., Pannill, F. C., & Tinetti, M. E. (1990). A simple procedure for general screening for functional disability in elderly patients. *Annals of Internal Medicine*, 112(9), 699–706.
- Laditka, S. B., & Laditka, J. N. (2002). Recent perspectives on active life expectancy for older women. *Journal of Women and Aging*, 14(1–2), 163–184.
- Lafont, C., Gérard, S., Voisin, T., Pahor, M., Vellas, B.; Members of I.A.G.G./A.M.P.A Task Force. (2011). Reducing “iatrogenic disability” in the hospitalized frail elderly. *Journal of Nutrition in Health & Aging*, 15(8), 645–660.
- Lally, F., & Crome, P. (2007). Understanding frailty. *Postgraduate Medicine Journal*, 83(975), 16–20.
- Landi, F., Abbatecola, A. M., Provonvoali, M., Corsonello, A., Bustacchini, S., Manigrasso, . . . Lattanzio, F. (2010). Moving against frailty: Does physical activity matter? *Biogerontology*, 11(5), 537–545. doi:10.1007/s10522-010-9296-1
- Landi, F., Onder, G., Cesari, M., Barillaro, C., Lattanzio, R., Ugo Carbonin, P., Bernabei, R., on behalf of the SILVERNET-HC Study Group. (2004). Comorbidity and social factors predicted hospitalization in frail elderly patients. *Journal of Clinical Epidemiology*, 57(8), 832–836.
- Landi, F., Russo, A., Liperoti, R., Tosato, M., Barillaro, C., Pahor, M., . . . Onder, G. (2010). Anorexia, physical function, and incident disability among the frail

- elderly population: Results from the iLSIRENTE study. *Journal of the American Medical Directors Association*, 11(4), 268–274.
- Lang, P. O., Heitz, D., Hédelin, G., Dramé, M., Jovenin, N., Ankri, J., . . . Blanchard, F. (2006). Early markers of prolonged hospital stays in older people: A prospective, multicenter study of 908 inpatients in french acute hospitals. *Journal of the American Geriatrics Society*, 54(7), 1031–1039.
- Lang, P. O., Michel, J. P., & Zekry, D. (2009). Frailty syndrome: A transitional state in a dynamic process. *Gerontology*, 55(5), 539–549.
- Lang, T. A., & Secic, M. (2006). *How to report statistics in medicine* (2nd ed.). Philadelphia, PA: American College of Physicians.
- Langford, C. P. H., Bowsher, J., Maloney, J. P., & Lillis, P. P. (1997). Social support: A conceptual analysis. *Journal of Advanced Nursing*, 25(1), 95–100.
- Lazarus, R. S., & Folkman, D. (1984). *Stress, appraisal, and coping*. New York, NY: Springer.
- Lee, D. H., Buth, K. J., Martin, B. J., Yip, A. A., & Hirsch, G. M. (2010). Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation*, 121(8), 973–978.
- Lee, P. G., Cigolle, C., & Blaum, C. (2009). The co-occurrence of chronic diseases and geriatric syndromes: The health and retirement study. *Journal of the American Geriatrics Society*, 57(3), 511–516.
- Lee, V., Fletcher, K., Westley, C., & Fankhauser, K. A. (2004). Competent to care: Strategies to assist staff in caring for elders. *Medsurg Nursing*, 13(5), 281–289.
- Lefevre, F., Feinglass, J., Potts, S., Soglin, L., Yarnold, P., Martin, G. J., & Webster, J. R. (1992). Iatrogenic complications in high risk elderly. *Archives of Internal Medicine*, 152(10), 2074–2080.
- Leidy, N. K., & Haase, J. E. (1996). Functional performance in people with chronic obstructive pulmonary disease: A qualitative analysis. *Advances in Nursing Science*, 18(3), 77–89.
- Lekan, D. (2009). Frailty and other emerging concepts in care of the aged. *Southern Online Journal of Nursing Research*, 9(3). Retrieved from [http://snrs.org/publications/SOJNR\\_articles2/Vol09Num03Art04.html](http://snrs.org/publications/SOJNR_articles2/Vol09Num03Art04.html)

- Lekan, D., Hendrix, C. C., McConnell, E. S., & White, H. (2010). The connected learning model for disseminating evidence-based care practices in clinical settings. *Nurse Educator in Practice, 10*(4), 243–248. doi:10.1016/j.nepr.2009.11.013
- Leng, S., Chaves, P., Koenig, K., & Walston, J. (2002). Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: A pilot study. *Journal of the American Geriatrics Society, 50*(7), 1268–1271.
- Leng, S., Xue, Q. L., Huang, Y., Semba, R., Chaves, P., Bandeen-Roche, K., . . . Walston, J. (2005). Total and differential white blood cell counts and their associations with circulating interleukin-6 levels in community-dwelling older women. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 60*(2), 195–199.
- Leng, S. X., Hung, W., Cappola, A. R., Yu, Q., Xue, Q. L., & Fried, L. P. (2009). White blood cell counts, insulin-like growth factor-1 levels, and frailty in community-dwelling older women. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 64*(4), 499–502.
- Leng, S. X., Xue, Q. L., Huang, Y., Ferrucci, L., Fried, L. P., & Walston, J. (2005). Baseline total and specific differential white blood cell counts and 5-year all-cause mortality in community-dwelling older women. *Experimental Gerontology, 40*(12), 982–987.
- Leng, S. X., Xue, Q. L., Tian, J., Huang, Y., Yeh, S. H., & Fried, L. P. (2009). Associations of neutrophil and monocyte counts with frailty in community-dwelling disabled older women: Results from the women's health and aging studies I. *Experimental Gerontology, 44*(8), 511–516.
- Leng, S. X., Xue, Q. L., Tian, J., Walston, J. D., & Fried, L. P. (2007). Inflammation and frailty in older women. *Journal of the American Geriatrics Society, 55*(6), 864–871.
- Lenze, E. J., Schulz, R., Martire, L. M., Zdaniuk, B., Glass, T., Kop, W. J., . . . Reynolds, C. F. (2005). The course of functional decline in older people with persistently elevated depressive symptoms: Longitudinal findings from the cardiovascular health study. *Journal of the American Geriatrics Society, 53*(4), 569–575.
- Leong, I. Y., Farrell, M. J., Helme, R. D., & Gibson, S. J. (2007). The relationship between medical comorbidity and self-rated pain, mood disturbance, and function in older people with chronic pain. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 62*(5), 550–555.

- Leung, J. M., Tsai, T. L., & Sands, L. P. (2011). Brief report: Preoperative frailty in older surgical patients is associated with early postoperative delirium. *Anesthesia Analgesia*, *112*(5), 1199–1201. doi:10.1213/ANE.0b013e31820c7c06
- Levenson, R. W., Cartensen, L. L., & Gottman, J. M. (1993). Long term marriage: Age, gender, and satisfaction. *Psychology and Aging*, *8*(2), 301–313.
- Levers, M. J., Estabrooks, C. A., & Ross Kerr, J. C. (2006). Factors contributing to frailty: Literature review. *Journal of Advanced Nursing*, *56*(3), 282–291.
- Levin, J. S. (1994). Religion and health: Is there an association, is it valid, and is it causal. *Social Science Medicine*, *38*(11), 1475–1482.
- Levin, J. S., Taylor, R. S., & Chatters, L. M. (1994). Race and gender differences in religiosity among older adults: Findings from four national surveys. *Journal of Gerontology*, *49*(3), S137–S145.
- Liao, S., & Ferrell, B. A. (2000). Fatigue in an older population. *Journal of the American Geriatrics Society*, *48*, 426–430.
- Lichtenberg, P. A., MacNeill, S. E., Lysack, C. L., Bank, A. L., & Neufeld, S. W. (2003). Predicting discharge and long-term outcome in older medical patients admitted to hospital. *Rehabilitation Psychology*, *48*(1), 37–43. doi:10.1037/0090-5550.48.1.37
- Lin, R. Y., Heacock, L. C., Bhargave, G. A., & Fogel, J. F. (2010). Clinical associations of delirium in hospitalized adult patients and the role of on admission presentation. *International Journal of Geriatric Psychiatry*, *25*(10), 1022–1029.
- Linares, L. F., Gomez-Reino, J. J., Carreira, P. E., Morillas, L., & Ibero I. (1986). C-reactive protein (CRP) levels in systemic lupus erythematosus (SLE). *Clinical Rheumatology*, *5*(1), 66–69.
- Lindhardt, T., Hallberg, I. R., & Poulsen, I. (2008). Nurses' experience of collaboration with relatives of frail elderly patients in acute hospital wards: A qualitative study. *International Journal of Nursing Studies*, *45*(5), 668–681.
- Lipsitz, L. A. (2004). Physiological complexity, aging, and the path to frailty. *Scientific Aging Knowledge Environment*, *21*(pe16). doi:10.1126/sageke.2004.16.pe16
- Lipsitz, L. A., & Goldberger, A. L. (1992). Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. *Journal of the American Medical Association*, *267*(13), 1806–1809.

- Logan, J. G., & Barksdale, D. J. (2008). Allostasis and allostatic load: Expanding the discourse on stress and cardiovascular disease. *Journal of Nursing and Healthcare of Chronic Illness* in association with *The Journal of Clinical Nursing*, 17(7b), 201–208.
- Loucks, E. B., Berkman, L. F., Gruenewald, T. L., & Seeman, T. E. (2006). Relation of social integration to inflammatory marker concentrations in men and women 70 to 79 years. *American Journal of Cardiology*, 97(7), 1010–1016.
- Loucks, E. B., Sullivan, L. M., D'Agostino, R. B. Sr., Larson, M. G., Berkman, L. F., & Benjamin, E. J. (2006). Social networks and inflammatory markers in the Framingham Heart Study. *Journal of Biosocial Science*, 38(6), 835–842.
- Lucicesare, A., Hubbard, R. E., Searle, S. D., & Rockwood, K. (2010). An index of self-rated health deficits in relation to frailty and adverse outcomes in older adults. *Aging Clinical and Experimental Research*, 22(3), 255–260.
- Lunney, J. R., Lynn, J., Foley, D. J., Lipson, S., & Guralnik, J. M. (2003). Patterns of functional decline at the end of life. *Journal of the American Medical Association*, 289(18), 2387–2392.
- Maggio, M., Guralnik, J. M., Longo, D. L., & Ferrucci, L. (2006). Interleukin-6 in aging and chronic disease: A magnificent pathway. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 61(6), 575–584.
- Mahoney, J. E. (1998). Immobility and falls. *Clinics in Geriatric Medicine*, 14(4), 699–726.
- Mahoney, E., Sager, M. A., & Jalaluddin, M. (1988). New walking dependence associated with hospitalization for acute medical illness: Incidence and significance. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 53(4), M307–M312.
- Main, C. J., Richards H. L., & Fortune, D. G. (2000). Why put new wine in old bottles: The need for a biopsychosocial approach to the assessment, treatment, and understanding of unexplained and explained symptoms in medicine. *Journal of Psychosomatic Research*, 48(6), 511–514.
- Makary, M. A., Segev, D. L., Pronovost, P. J., Syin, D., Bandeen-Roche, K., Patel, P., . . . Fried, L. P. (2010). Frailty as a predictor of surgical outcomes in older patients. *Journal of the American College of Surgery*, 210(6), 901–908.
- Maloney, E. M., Boneva, R., Nater, U. M., & Reeves, W. C. (2009). Chronic fatigue syndrome and high allostatic load: Results from a population-based case-control

- study in Georgia. *Psychosomatic Medicine*, 71(5), 549–556.  
doi:10.1097/PSY.0b013e3181a4fea8
- Mancini, A. D., & Bonanno, G. A. (2006). Marital closeness, functional disability, and adjustment in late life. *Psychology and Aging*, 21(3), 600–610.
- Manton, K. G. (2008). Recent declines in chronic disability in the elderly U.S. population: Risk factors and future dynamics. *Annual Review of Public Health*, 29, 91–113.
- Manty, M., Mendes de Leon, C. F., Rantanen, T., Era, P., Pedersen, A. N., Ekman, A., . . . Avlund, K. (2012). Mobility-related fatigue, walking speed, and muscle strength in older people. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 67(5), 523–529.
- Marcantonio, E. R., McKean, S., Goldfinger, M., Kleefield, S., Yurkofsky, M., & Brennan, T. A. (1999). Factors associated with unplanned hospital readmission among patients 65 years of age and older in a medicare managed care plan. *American Journal of Medicine*, 107(1), 13–17.
- Markle-Reid, M., & Browne, G. (2003). Conceptualizations of frailty in relation to older adults. *Journal of Advanced Nursing*, 44(1), 58–68.
- Marzetti, E., & Leeuwenburgh, C. (2006). Skeletal muscle apoptosis, sarcopenia, and frailty at old age. *Experimental Gerontology*, 41(12), 1234–1238.
- Matteson, M. A., & McConnell, E. S. (Eds.). (1985). *Gerontological nursing: Concepts and practice*. Philadelphia, PA: W. B. Saunders.
- Maxwell, C. J., Dalby, D. M., Slater, M., Patten, S. B., Hogan, D. B., Eliasziw, M., & Herdes, J. P. (2008). The prevalence and management of current daily pain among older home care clients. *Pain*, 138(1), 208–216.  
doi:org/10.1016/j.pain.2008.04.007
- McConnell, E.S., Lekan, D., Bunn, M., Egerton, E., Corazzini, K.N., Hendrix, C.D., Bailey, D.E., Jr. (2009). Teaching evidence-based nursing practice in geriatric care settings: The geriatric nursing innovations through education institute. *Journal of Gerontological Nursing*, 35(4), 26-33.
- McDermid, R. C., Stelfox, H. T., & Bagshaw, S. M. (2011). Frailty in the critically ill: A novel concept. *Critical Care*, 15(1), 301. doi:10.1186/cc9297
- McDougall, G.J., & Balyer, J. (1998). Decreasing mental frailty in at-risk elders. *Geriatric Nursing*, 19(4), 220-224.

- McEwen, B. S. (1993). Stress and the individual. Mechanisms leading to disease. *Archives of Internal Medicine*, *153*(18), 2093–2101.
- McEwen, B. S. (2003a). Interacting mediators of allostasis and allostatic load: Towards an understanding of resilience in aging. *Metabolism*, *52*, 10–16.
- McEwen, B. S. (2003b). Mood disorders and allostatic load. *Biological Psychiatry*, *54*(3), 200–207.
- McEwen, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology*, *583*(2–3), 174–185.
- McEwen, B. S., & Lasley, E. N. (2003). Allostatic load: When protection gives way to damage. *Advances in Mind-Body Medicine*, *19*(1), 28–33.
- McEwen, B. S., & Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Archives of Internal Medicine*, *153*(18), 2093–2101.
- McEwen, B. S., & Wingfield, J. C. (2010). What is in a name? Integrating homeostasis, allostasis and stress. *Hormones and Behavior*, *57*(2), 105–111.
- McDermid, R. C., Stelfox, H. T., & Bagshaw, S. M. (2011). Frailty in the critically ill: A novel concept. *Critical Care*, *15*(1), 301. doi:10.1186/cc9297
- MedicineNet.com. (2012). Anorexia. Retrieved from <http://www.medterms.com/script/main/art.asp?articlekey=2268>
- Mezey, M., & Fulmer, T. (1998). Quality care for the frail elderly. *Nursing Outlook*, *46*(6), 291–292.
- Mezey, M., Kobayashi, M., Grossman, S., Firpo, A., Fulmer, T., & Mitty, E. (2004). Nurses Improving Care to Health System Elders (NICHE): Implementation of best practice models. *Journal of Nursing Administration*, *34*(10), 451–457.
- Mezey, M. D., & Mitty, E. (2011). A bill of rights for hospitalized older adults. *Journal of Nursing Administration*, *41*(3), 115–121. doi:10.1097/NNA.0b013e31820c722d
- Mezuk, B., Edwards, L., Lohman, M., Choi, M., & Lapane, K. (2011). Depression and frailty in later life: A synthetic review. *International Journal of Geriatric Psychiatry*, *27*(9), 879–892. doi:10.1002/gps.2807

- Miles, T. P., Palmer, R. F., Espino, D. V., Mouton, C. P., Lichtenstein, M. J., & Markides, K. S. (2001). New-onset incontinence and markers of frailty: Data from the hispanic established populations for epidemiologic studies of the elderly. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 56(1), M19–M24.
- Min, L. C., Elliott, M. N., Wenger, N. S., & Saliba, D. (2006). Higher vulnerable elders survey scores predict death and functional decline in vulnerable older people. *Journal of the American Geriatrics Society*, 54(3), 507–511.
- Mitnitski, A., Fallah, N., Rockwood, M. R., & Rockwood, K. (2011). Transitions in cognitive status in relation to frailty in older adults: A comparison of three frailty measures. *Journal of Nutrition in Health and Aging*, 15(10), 863–867.
- Mitnitski, A. B., Graham, J. E., Mogilner, A. J., & Rockwood, K. (2002). Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC Geriatrics*, 27(2), 1.
- Mitnitski, A. B., Mogilner, A. J., MacKnight, C., & Rockwood, K. (2002). The mortality rate as a function of accumulated deficits in a frailty index. *Mechanisms of Ageing Development*, 123(11), 1457–1460.
- Mitnitski, A., Mogilner, A., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *Scientific World Journal*, 1, 323–336.
- Mitnitski, A., Song, X. A., & Rockwood, K. (2004). The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 59(6), 627–632.
- Mitnitski, A., Song, X. A., & Rockwood, K. (2007). Improvement and decline in health status from late life age: Modeling age-related changes in deficit accumulation. *Experimental Gerontology*, 42(11), 1109–1115.
- Mitty, E. (2010). Iatrogenesis, frailty and geriatric syndromes. *Geriatric Nursing*, 31(5), 368–374.
- Mohandas, A., Reifsnnyder, J., Jacobs, M., & Fox, T. (2011). Current and future directions in frailty research. *Population Health Management*, 14(6), 277–283.
- Mohile, S. G., Xian, Y., Dale, W., Fisher, S. G., Rodin, M., Morrow, G. R., . . . Hall, W. (2009). Association of cancer diagnosis with vulnerability and frailty in older medicare beneficiaries. *Journal of the National Cancer Institute*, 101(17), 1206–1215.

- Molina-Garrido, M. J., & Guillen-Ponce, C. (2010). Comparison of two frailty screening tools in older women with early breast cancer. *Critical Reviews in Oncology and Hematology*, 79(1), 51–64. doi:10.1016/j.critrevonc.2010.06.004
- Montero-Odasso, M., Muir, S. W., Hall, M., Doherty, T. J., Kloseck, M., Beutchet, O., & Speechley, M. (2011). Gait variability is associated with frailty in community-dwelling older adults. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 66(5), 568–576.
- Montesanto, A., Lagani, V., Martino, C., Dato, S., De Rango, F., Berardelli, M., . . . Passarino, G. (2010). A novel, population-specific approach to define frailty. *Age*, 32(3), 385–395. doi:10.1007/s11357-010-9136-x
- Mor, V. (2005). The compression of morbidity hypothesis: A review of research and prospects for the future. *Journal of the American Geriatrics Society*, 53(9 Suppl.), S308–S309.
- Morley, J. E. (2010). Anorexia, weight loss, and frailty. *Journal of the American Medical Directors Association*, 11(4), 225–228. doi:10.1016/j.jamda.2010.02.005
- Morley, J. E., Haren, M. T., Rolland, Y., & Kim, M. J. (2006). Frailty. *Medical Clinics of North America*, 90(5), 837–847.
- Mullings, L. (2005). Resistance and resilience: The sojourner syndrome and the social context of reproduction in central Harlem. *Transforming Anthropology*, 13(2), 79–91.
- Murphy, T. E., Agostini, J. V., Van Ness, P. H., Peduzzi, P., Tinetti, M. E., & Allore, H. G. (2008). Assessing multiple medication use with probabilities of benefits and harms. *Journal of Aging Health*, 20(6), 694–709. doi:10.1177/0898264308321006.
- Murray, A. M., Levkoff, S. E., Wetle, T. T., Beckett, L., Cleary, P. D., Schoor, J. D., . . . Evans, D. A. (1993). Acute delirium and functional decline in the hospitalized elderly patient. *Journal of Gerontology*, 48(5), M181–M186.
- Musick, J. A. (1996). Religion and subjective health among black and white elders. *Journal of Health and Social Behavior*, 37(3), 221–237.
- Nagi, S. Z. (1976). An epidemiology of disability among adults in the United States. The Milbank Memorial Fund Quarterly. *Health and Society*, 54(4), 439–467.
- NANDA International. (2011). NANDA-I nursing diagnoses: Definitions and classification, 2012–2014 (9th ed.). Hoboken, NJ: Wiley-Blackwell.

- Nash, C. B. (2008). *Identifying frailty using the ICT: Proof of concept*. (Thesis). Library and Archives Canada. Published Heritage Branch. Ontario, Canada. ISBN: 978-0-494-48051-9.
- National Institute on Aging. (1991). *Physical frailty: A reducible barrier to independence for older Americans*. (NIH Publication No. 91-397). Washington, DC: US Government Printing Office.
- National Institute on Aging (NIA). (2004). *NIA workshop on inflammation, inflammatory mediators, and aging. Workshop summary*. National Institute on Aging, National Institutes of Health, Department of Health and Human Services. Bethesda, MD. September 1–2, 2004.
- National Institutes of Health. (2012). Frailty and independence. Age Pages: National Institutes on Aging Booklets. *Research for a New Age, NIH Publication No. 93-1129*. Washington, DC: U.S. Government Printing Office. Retrieved from [http://www.healthandage.com/html/min/nih/content/booklets/research\\_new\\_age/page7.htm](http://www.healthandage.com/html/min/nih/content/booklets/research_new_age/page7.htm)
- Naylor, M.D., Kurtzman, E.T., Grabowski, D.C., Harrington, C., McClellan, M., & Reinhard, S.C. (2012). Unintended consequences of steps to cut readmissions and reform payment may threaten care of vulnerable older adults. *Health Affairs*, *31*(7), 1623-1632. doi:10.1377/hlthaff.2012.0110
- Nelson, J. J., Liao, D., Sharrett, A. R., Folsom, A. R., Chambless, L. E., Shahar, E., . . . Heiss, G. (2000). Serum albumin level as a predictor of incident coronary heart disease: The Atherosclerosis Risk in Communities (ARIC) study. *American Journal of Epidemiology*, *151*(5), 468–477.
- Nelson, J. M., Dufraux, K., & Cook, P. F. (2007). The relationship between glycemic control and falls in older adults. *Journal of the American Geriatrics Society*, *55*(12), 2041–2044.
- Newbern, V. B., & Krowchuk, H. V. (1994). Failure to thrive in elderly people: A conceptual analysis. *Journal of Advanced Nursing*, *19*(5), 840–849.
- Newman, A. B., Bayles, C. M., Milas, C. N., McTigue, K., Williams, K., Robare, J. F., . . . Kuller, L. H. (2010). The 10 keys to healthy aging: Findings from an innovative prevention program in the community. *Journal of Aging and Health*, *22*(5), 547–566.
- Newman, A. B., Gottdiener, J. S., Mcburnie, M. A., Hirsch, C. H., Kop, W. J., Tracy, R., . . . Fried, L. P.; the Cardiovascular Health Study Research Group. (2001). Associations of subclinical cardiovascular disease with frailty. *Journals of*

*Gerontology. Series A, Biologic Sciences and Medical Sciences*, 56(3), M158–166.

Newsom, J. T., & Schulz, R. (1996). Social support as a mediator in the relation between functional status and quality of life in older adults. *Psychology of Aging*, 11(1), 34–44.

Ndumele, C. E., Pradhan, A. D., & Ridker, P. M. (2006). Interrelationships between inflammation, c-reactive protein, and insulin resistance. *Journal of Cardiometabolic Syndrome*, 1(3), 190–196.

Ní Mhaoláin, A. M., Fan, C. W., Romero-Ortuno, R., Cogan, L., Cunningham, C., Lawlor, B., & Kenny, R. A. (2012). Depression: A modifiable factor in fearful older fallers transitioning to frailty? *International Journal of Geriatric Psychiatry*, 27(7), 727–733. doi:10.1002/gps.2780

Nicholson, C., Meyer, J., Flatley, M., & Holman, C. (2012). The experience of living at home with frailty in old age: A psychosocial qualitative study. *International Journal of Nursing Studies*. [Epub head of print]. doi:10.1016/j.ijnurstu.2012.01.006

Nicholson, C., Meyer, J., Flatley, M., Holman, C., & Lowton, K. (2012). Living on the margin: Understanding the experience of living and dying with frailty in old age. *Social Science & Medicine*, 75(8), 1426–1432.

Nicklett, E. J., Semba, R. D., Simonsick, E. M., Szanton, S., Bandeen-Roche, K., Ferrucci, L., . . . Fried, L. P. (2012). Diet quality and social support: Factors associated with serum carotenoid concentrations among older disabled women (the women's health and aging study). *Journal of Nutrition, Health, & Aging*, 16(6), 511–518.

Nicolson, N., Storms, C., Ponds R., & Sulon, J. (1997). Salivary cortisol levels and stress reactivity in human aging. *Journals of Gerontology. Series A, Biologic Sciences and Medical Sciences*, 52(2), M68–M75.

Nicolson, N. A., & van Diest, R. (2000). Salivary cortisol patterns in vital exhaustion. *Journal of Psychosomatic Research*, 49(5), 335–342.

Nielsen, L., Seeman, T., & Hahn, A. (2007). *NIA exploratory workshop on allostatic load*. Behavioral and Social Research Program, National Institute on Aging, National Institutes of Health. Washington, DC, November 29–30, 2007.

North Carolina Institute of Medicine (NC-IOM). (2011). *Healthy North Carolina 2020 technical report*. Morrisville, NC: North Carolina Institute of Medicine; 2011.

Retrieved from <http://www.nciom.org/wp-content/uploads/2011/01/HNC2020-TechReport-final.pdf>

- Nowak, A., & Hubbard, R. E. (2009). Falls and frailty: Lessons from complex systems. *Journal of the Royal Society of Medicine*, 102(3), 98–102.
- Nalysnyk, L., Fahrbach, K., Reynolds, M. W., Zhao, S. Z., & Ross, S. (2003). Adverse events in coronary artery bypass graft (CABG) trials: A systematic review and analysis. *Heart*, 89(7), 767–772.
- O’Connell, B., Hawkins, M. T., Baker, L., & Ostaszkiwicz, J. (2011). Care needs and functional status of older acute care patient. *Research in Gerontological Nursing*, 4(4), 271–279. doi:10.3928/19404921-20110201-02
- Oda, E., & Kawai, R. (2010). Comparison between high-sensitivity c-reactive protein (hs-CRP) and white blood cell count (WBC) as an inflammatory component of metabolic syndrome in Japanese. *Internal Medicine*, 49(2), 117–124.
- Okamura, T., Hayakawa T., Hozawa, A., Kadowaki, T., Murakami, Y., Kita, Y., . . . Ueshima, H., for the NIPPON DATA80 Research Group. (2008). Lower levels of serum albumin and total cholesterol associated with decline in activities of daily living and excess mortality in a 12-year cohort study of elderly Japanese. *Journal of the American Geriatrics Society*, 56(3), 529–535.
- Olivares, M., Hertrampf, E., Capurro, M. T., & Wegner, D. (2000). Prevalence of anemia in elderly subjects living at home: Role of micronutrient deficiency and inflammation. *European Journal of Clinical Nutrition*, 54(11), 834–839.
- Olson, E. V., Johnson, B. J., & Thompson, L. F. (1990). The hazards of immobility. 1967. *American Journal of Nursing*, 90(3), 43–48.
- Ostir, G.V., Berges, I., Kuo, Y.F., Goodwin, J.S., Ottenbacher, K.J., & Guralnik, J.M. (2012). Assessing gait speed in acutely ill older patients admitted to an acute care for elders hospital unit. *Archives of Internal Medicine*, 172(4), 353-358. doi:10.1001/archinternmed.2011.1615
- Ostir, O., Kenneth, J. I., & Markides, K. (2004). Onset of frailty in older adults and the protective role of positive affect. *Psychology and Aging*, 19(3), 402–408.
- Otterness, I. G. (1994). The value of c-reactive protein measurement in rheumatoid arthritis. *Seminars in Arthritis and Rheumatology*, 24(2), 91–104.
- Ouslander, J. G., & Berenson, R. A. (2011). Reducing unnecessary hospitalizations of nursing home residents. *New England Journal of Medicine*, 365(13), 1165–1167.

- Ozaki, A., Uchiyama, M., Tagaya, H., Ohida, T., & Ogihara, R. (2007). The Japanese centenarian study: Autonomy was associated with health practices as well as physical status. *Journal of the American Geriatrics Society*, *55*(1), 95–101.
- Page, R. L., Linnebur, S. A., Bryant, L. L., & Ruscin, J. M. (2010). Inappropriate prescribing in the hospitalized elderly patient: Defining the problem, evaluation tools, and possible solutions. *Clinical Interventions in Aging*, *5*, 75–87.
- Paixao, C. M., & Pruger de Queiroz Campos Araujo, A. (2010). Frailty and vulnerability: Are the two terms equivalent in paediatrics and geriatrics? *European Geriatric Medicine*, *1*, 166–169. doi:10.1016/j.eurger.2010.05.002
- Palmore, E. (1977). Facts on aging. A short quiz. *Gerontologist*, *17*(4), 315–320.
- Palmore, E. (2004). Ageism in Canada and the United States. *Journal of Cross-Cultural Gerontology*, *19*, 41–46.
- Palmer, R. M., Counsell, S., & Landefeld, C. S. (1998). Clinical intervention trials: The ACE unit. *Clinics in Geriatric Medicine*, *14*(4), 831–849.
- Pancorbo-Hidalgo, P. L., Garcia-Fernandez, F. P., Lopez-Medina, I. M., & Alvarez-Nieto, C. (2006). Risk assessment scales for pressure ulcer prevention: A systematic review. *Journal of Advanced Nursing*, *54*(1), 94–110.
- Panno, J. M., Kolcaba, K., & Holder, C. (2000). Acute care for elders (ACE): A holistic model for geriatric orthopaedic nursing care. *Orthopedic Nursing*, *19*(6), 53–60.
- Panza, F., Solfrizzi, V., Frisardi, V., Maggi, S., Sancarlo, D., Adante, F., . . . Pilotto, A. (2011). Different models of frailty in predementia and dementia syndromes. *Journal of Nutrition, Health, & Aging*, *15*(8), 711–719.
- Parmelee, P. A., Lawton, M. P., & Katz, I. R. (1998). The structure of depression among elderly institution residents: Affective and somatic correlates of physical frailty. *Journal of Gerontology. Series A, Biologic Sciences and Medical Sciences*, *53*(2), M155–M162.
- Patel, K. V. (2008). Epidemiology of anemia in older adults. *Seminars in Hematology*, *45*(4), 210–217. doi:10.1053/j.seminhematol.2008.06.006
- Patel, K. V., Harris, T. B., Faulhaber, M., Angleman, S. B., Connelly, S., Bauer, D. C., . . . Guralnik, J. M. (2007). Racial variation in the relationship of anemia with mortality and mobility disability among older adults. *Blood*, *109*(11), 4663–4670.

- Peek, M. K., Howrey, B. T., Ternent, R. S., Ray, L. A., & Ottenbacher, K. J. (2012). Social support, stressors, and frailty among older Mexican American adults. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, 67(6), 755–764. doi:10.1093/geronb/gbs081
- Pel-Little, R. E., Schuurmans, M. J., Emmelot-Vonk, M. H., & Verhaar, H. J. (2009). Frailty: Defining and measuring of a concept. *Journal of Nutrition, Health, & Aging*, 13(4), 390–394.
- Penninx, B. W., Kritchevsky, S. B., Newman, A. B., Nicklas, B. J., Simonsick, E. M., Rubin, S., . . . Pahor, M. (2004). Inflammatory markers and incident mobility limitation in the elderly. *Journal of the American Geriatrics Society*, 52(7), 1105–1113.
- Pepys, M. B., & Hirschfield, G. M. (2003). C-reactive protein: A critical update. *The Journal of Clinical Investigation*, 111(12), 1805–1812.
- Perera, V., Hilmer, S. N., & McLachlan, A. J. (2010). Frailty scales should be using validated scales. *Drugs and Aging*, 27(8), 687.
- Peterson, M., Giuliani C., Morey, M. C., Pieper, C. F., Evenson, K. R., Mercer, V., . . . Simonsick, E.M.; The Health, Aging and Body Composition Study Research Group. (2009). Physical activity as a preventative factor for frailty: The health, aging, and body composition study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 64(1), 61–68.
- Phan, H. M., Alpert, J. S., & Fain, M. (2008). Frailty, inflammation, and cardiovascular disease: Evidence of a connection. *American Journal of Geriatric Cardiology*, 17(2), 101–117.
- Pfaff, J. (2002). The geriatric resource nurse model: A culture change. *Geriatric Nursing*, 23(3), 140–144.
- Phillipson, C. (2002). The frailty of old age. In M. Davis (Ed.), *The Blackwell companion to social work* (2nd ed., pp. 58–63). Oxford, UK: Blackwell.
- Pijpers, E., Ferreira, I., Stehouwer, C.D., & Nieuwenhuijzen Kruseman, A.C. (2012). The frailty dilemma. Review of the predictive accuracy of major frailty scores. *European Journal of Internal Medicine*, 23(2), 118–123. doi:10.1016/j.ejim.2011.09.003
- Pilotto, A., Rengo, F., Marchionni, N., Sancarlo, D., Fontana, A., Panza, F., & Ferrucci, L.; FIRI-SIGG Study Group. (2012). Comparing the prognostic accuracy for all-

cause mortality of frailty instruments: A multicentre 1-year follow-up in hospitalized older patients. *PLoS One*, 7(1), e29090.

- Pine, Z. M., Gurland, B., & Chren, M. M. (2000). Report of having slowed down: Evidence for the validity of a new way to inquire about mild disability in elders. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 55(7), M378–M383.
- Pol, R. A., van Leeuwen, B. L., Visser, L., Izaks, G. J., van den Dungen, J. J., Tielliu, I. F., & Zeebregts, C. J. (2011). Standardised frailty indicator as predictor for postoperative delirium after vascular surgery: A prospective cohort study. *European Journal of Vascular and Endovascular Surgery*, 42(6), 824–830.
- Potts, S., Feinglass, J., Lefevre, F., Kadah, H., Branson, C., & Webster, J. (1993). A quality-of-care analysis of cascade iatrogenesis in frail elderly hospital patients. *QRB Quality Review Bulletin*, 19(6), 199–205.
- Purser, J. L., Golightly, Y. M., Feng, Q., Helmick, C. G., Renner, J. B., & Jordan, J. M. (2012). Association of slower walking speed with incident knee osteoarthritis-related outcomes. *Arthritis Care & Research*, 64(7), 1028–1035. doi:10.1002/acr.21655
- Purser, J., Kuchibhatla, M. N., Fillenbaum, G. G., Harding, T., Peterson, E. D., & Alexander, K. P. (2006). Identifying frailty in hospitalized older adults with significant coronary artery disease. *Journal of the American Geriatrics Society*, 54(11), 1674–1678.
- Purser, J. L., Weinberger, M., Cohen, H. J., Pieper, C. F., Morey, M. C, Li, T., . . . Lapuerta, P. (2005). Walking speed predicts health status and hospital costs for frail elderly male veterans. *Journal of Rehabilitation Research Development*, 42(4), 535–546.
- Puts, M. T., Lips, P., & Deeg, D. J. (2005a). Sex differences in the risk of frailty for mortality independent of disability and chronic diseases. *Journal of the American Geriatrics Society*, 53(1), 40–47.
- Puts, M. T., Lips, P., & Deeg, D. J. (2005b). Static and dynamic measures of frailty predicted decline in performance-based and self-reported physical functioning. *Journal of Clinical Epidemiology*, 58(11), 1188–1198.
- Puts, M. T., Monette, J., Girre, V., Pepe, C., Monette, M., Assouline, S., . . . Bergman, H. (2011). Are frailty markers useful for predicting treatment toxicity and mortality in older newly diagnosed cancer patients? Results from a prospective pilot study. *Clinical Reviews in Oncology/Hematology*, 78(2), 138–149.

- Puts, M. T., Monette, J., Girre, V., Wolfson, C., Monette, M., Batist, G., & Bergman, H. (2010). Does frailty predict hospitalization, emergency department visits, and visits to the general practitioner in older newly-diagnosed cancer patients? Results of a prospective pilot study. *Critical Reviews in Oncology /Hematology*, 76(2), 142–151.
- Puts, M. T., Shekary, N., Widdershoven, G., Heldens, J., Lips, P., & Deeg, D. J. (2007). What does quality of life mean to older frail and non-frail community-dwelling adults in the Netherlands? *Quality of Life Research*, 16(2), 263–277.
- Puts, M. T., Visser, M., Twisk, J. W., Deeg, D. J., & Lips, P. (2005). Endocrine and inflammatory markers as predictors of frailty. *Clinical Endocrinology*, 63(4), 403–411.
- Quinlan, N., Marcantonio, E. R., Inouye, S. K., Gill, T. M., Kamholz, B., & Rudolph, J. L. (2011). Vulnerability: The crossroads of frailty and delirium. *Journal of the American Geriatrics Society*, 59(Suppl 2), S262–S268. doi:10.1111/j.1532-5415.2011.03674.x
- Ranjit, N., Diez-Roux, A. V., Shea, S., Cushman, M., Seeman, T., Jackson, S. A., & Ni, H. (2007). Psychosocial factors and inflammation in the multi-ethnic study of atherosclerosis. *Archives of Internal Medicine*, 167(2), 174–181.
- Ranjit N., Diez-Roux, A. V., Shea, S., Cushman, M., Ni, H., & Seeman, T. (2007). Socioeconomic position, race/ethnicity, and inflammation in the multi-ethnic study of atherosclerosis. *Circulation*, 116(21), 2383–2390.
- Rantz, M. J., Marek, K. D., & Zwygart-Stauffacher, M. (2000). The future of long-term care for the chronically ill. *Nursing Administration Quarterly*, 25(1), 51–58.
- Raphael, D., Cava, M., Brown, I., Renwick, R., Heathcote, K., Weir, N., . . . Kirwan, L. (1995). Frailty: A public health perspective. *Canadian Journal of Public Health*, 86(4), 224–227.
- Rapuri, P. B., Gallagher, J. C., & Smith, L. M. (2007). Smoking is a risk factor for decreased physical performance in elderly women. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(1), 93–100.
- Rastogi, R., & Meek, B. D. (2013). Management of chronic pain in elderly, frail patients: Finding a suitable, personalized method of control. *Clinical Interventions in Aging*, 8, 37–46. doi:10.2147/CIA.S30165.
- Raudonis, B. M., & Daniel, K. (2010). Frailty: An indication for palliative care. *Geriatric Nursing*, 31(5), 379–384.

- Ravaglia, G., Forti, P., Lucicesare, A., Pisacane, N., Rietti, E., . . . Patterson, C. (2008). Development of an easy prognostic score for frailty outcomes in the aged. *Age & Ageing*, *37*(2), 161–166.
- Reuben, D. B., Judd-Hamilton, L., Harris, T. B., & Seeman, T. E.; MacArthur Studies of Successful Aging. (2003). The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur studies of successful aging. *Journal of the American Geriatrics Society*, *51*(8), 1125–1130.
- Reuben, D. B., Ferrucci, L., Wallace, R., Tracy, R. P., Corti, M. C., Heimovitz, H., & Harris, T. B. (2000). The prognostic value of serum albumin in healthy older persons with low and high serum interleukin-6 (IL-6) levels. *Journal of the American Geriatric Society*, *48*(11), 1404–1407.
- Reuben, D. B., Cheh, A. I., Harris, T. B., Ferrucci, L., Rowe, J. W., Tracy, R. P., & Seeman, T. E. (2002). Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons. *Journal of the American Geriatrics Society*, *50*(4), 638–644.
- Retornaz, F., Monette, J., Batist, G., Monette, M., Sourial, N., Small, D., . . . Bergman, H. (2008). Usefulness of frailty markers in the assessment of the health and functional status of older cancer patients referred for chemotherapy: A pilot study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *63*(5), 518–522.
- Retornaz, F., Potard, I., Molines, C., & Rousseau, F. (2011). What is frailty in geriatric oncology? *Oncologie*, *13*(2–3), 73–77. doi:10.1007/s10269-011-1993-4
- Rice, K. L., Bennett, M., Gomez, M., Theall, K. P., Knight, M., & Foreman, M. D. (2011). Nurses' recognition of delirium in the hospitalized older adult. *Clinical Nurse Specialist*, *25*(6), 299–311. doi:10.1097/NUR.0b013e318234897b
- Rigney, T. (2010). Allostatic load and delirium in the hospitalized older adult. *Nursing Research*, *59*(5), 322–330.
- Robertson, R. G., & Montagnini, M. (2004). Geriatric failure to thrive. *American Family Physician*, *70*(2), 343–350.
- Robinson, T. N., Eiseman, B., Wallace, J. I., Church, S. D., McFann, K. K., Pfister, S. M., . . . Moss, M. (2009). Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. *Annals of Surgery*, *250*(3), 449–455.
- Robinson, T. N., Wallace, J. I., Wu, D. S., Wiktor, A., Pointer, L. F, Pfister, S. M., . . . Moss, M. (2011). Accumulated frailty characteristics predict postoperative

- discharge institutionalization in the geriatric patient. *Journal of the American College of Surgery*, 213(1), 37–42. doi.org/10.1016/j.jamcollsurg.2011.01.056
- Robinson, T. N., Wu, D. S., Stiegmann, G. V., & Moss, M. (2011). Frailty predicts increased hospital and six-month healthcare cost following colorectal surgery in older adults. *American Journal of Surgery*, 202(5), 11–14.
- Robinson, A., & Street, A. (2004). Improving networks between acute care nurses and an aged care assessment team. *Journal of Clinical Nursing*, 13(4), 486–496.
- Rockwood, K. (2005). What would make a definition of frailty successful? *Age and Ageing*, 34(5), 432–434.
- Rockwood, K., Andrew, M., & Mitnitski, A. (2007). A comparison of two approaches to measuring frailty in elderly people. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7), 738–743.
- Rockwood, K., & Bergman, H. (2012). FRAILTY: A report from the 3(rd) joint workshop of IAGG/WHO/SFGG, Athens, January 2012. *Canadian Geriatrics Journal*, 15(2), 31–36. doi: 10.5770/cgj.15.35
- Rockwood, K., Fox, R. A., Stolee, P., Robertson, D., & Beattie, B. L. (1994). Frailty in elderly people: An evolving concept. *Canadian Medical Association*, 150(4), 489–495.
- Rockwood, K., Howlett, S. E., MacKnight, C., Beattie, B. L., Bergman, H., Hebert, R., . . . McDowell, I. (2004). Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: Report from the Canadian study of health and aging. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 59(12), 1310–1317.
- Rockwood, K., Hogan, D. B., & MacKnight, C. (2000). Conceptualization and measurement of frailty in elderly people. *Drugs and Aging*, 17(4), 295–302.
- Rockwood, K., & Hubbard, R. (2004). Frailty and the geriatrician. *Age & Ageing*, 33(5), 429–430.
- Rockwood, K., & Mitnitski, A. (2007). Geriatric syndromes. *Journal of the American Geriatrics Society*, 55(12), 2092.
- Rockwood, K., & Mitnitski, A. (2011). Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clinics in Geriatric Medicine*, 27, 17–26.

- Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal*, *173*(5), 489–495.
- Rockwood, K., Song, X., & Mitnitski, A. (2011). Changes in relative fitness and frailty across the adult lifespan: Evidence from the Canadian national population health survey. *Canadian Medical Association Journal*, *183*(8), E487–E494.
- Rockwood, K., Stadnyk, K., MacKnight, C., McDowell, I., Hébert R., & Hogan, D. B. (1999). A brief clinical instrument to classify frailty in elderly people. *Lancet*, *353*(9148), 205–206.
- Rodríguez-Mañas, L., Féart, C., Mann, G., Viña, J., Chatterji, S., Chodzko-Zajko, W., . . . Vega E; on behalf of the FOD-CC group (Appendix 1). (2012). Searching for an operational definition of frailty: A delphi method based consensus statement. The frailty operative definition-consensus conference project. *Journals of Gerontology. Series A, Biological Sciences & Medical Sciences*, *68*(1), 62–67. doi:10.1093/gerona/gls119
- Roe, B., Watson, N. M., Palmer, M. H., Mueller, C., Vinsnes, A. G., & Wells M. (2004). Translating research on incontinence into practice. *Nursing Research*, *53*(6 Suppl), S56–S60.
- Rolfson, D. B., McElhaney, J. E., Rockwood, K., Finnega, B. A., Entwistle, L. M., Wong, J. F., & Suarez-Almazor, M. E. (1999). Incidence and risk factors for delirium and other adverse outcomes in older adults after coronary artery bypass graft surgery. *Canadian Journal of Cardiology*, *15*(7), 771–776.
- Romero-Ortuno, R. (2013). The frailty instrument for primary care of the survey of health, ageing and retirement in Europe predicts mortality similarly to a frailty index based on comprehensive geriatric assessment. *Geriatrics & Gerontology International*, *13*(2), 497–504. doi:10.1111/j.1447-0594.2012.00948.x
- Romero-Ortuno, R., Walsh, C. D., Lawlor, B. A., & Kenny, R. A. (2010). A frailty instrument for primary care: Findings from the survey of health, ageing and retirement in Europe (SHARE). *BMC Geriatrics*, *24*(10), 57. doi:10.1186/1471-2318-10-57
- Rønning, B., Wyller, T. B., Seljeflot, I., Jordhøy, M. S., Skovlund, E., Nesbakken, A., & Kristjansson, S. R. (2010). Frailty measures, inflammatory biomarkers and post-operative complications in older surgical patients. *Age & Ageing*, *39*(6), 758–761.
- Roth, K. S. (2001). Detecting ‘failure to thrive.’ *Nursing Homes: Long Term Care Management*, *50*(10), 60.

- Rothman, M. D., Leo-Summers, L., & Gill, T. M. (2008). Prognostic significance of potential frailty criteria. *Journal of the American Geriatrics Society*, *56*(12), 2211–2216.
- Roy, C. N. (2011). Anemia in frailty. *Clinics in Geriatric Medicine*, *27*(1), 67–78. doi:10.1016/j.cger.2010.08.005
- Rozzini, R., Frisoni, G. B., Franzoni, S., & Trabucchi, M. (2000). Change in functional status during hospitalization in older adults: A geriatric concept of frailty. *Journal of the American Geriatrics Society*, *48*(8), 1024–1025.
- Rubenstein, L. Z. (2006). Falls in older people: Epidemiology, risk factors and strategies for prevention. *Age and Ageing*, *35*(S2), ii37–ii41. doi:10.1093/ageing/af1084
- Runge, M., & Hunter, G. (2006). Determinants of musculoskeletal frailty and the risk of falls in old age. *Journal of Musculoskeletal and Neuronal Interactions*, *6*(2), 167–173.
- Sager, M. A., & Rudberg, M. A. (1998). Functional decline associated with hospitalization for acute illness. *Clinics in Geriatric Medicine*, *14*(4), 669–679.
- Saliba, D., Elliott, M., Rubenstein, L. Z., Solomon, D. H., Young, R. T., Kamberg, C. J., . . . Wenger, N. S. (2001). The vulnerable elders survey: A tool for identifying vulnerable older people in the community *Journal of the American Geriatrics Society*, *49*(12), 1691–1699.
- Samper-Ternent, R., Karmarkar, A., Graham, J., Reistetter, T., & Ottenbacher, K. (2011). Frailty as predictor of falls in older Mexican Americans. *Journal of Aging & Health*, *24*(2), 641–53. doi:10.1177/0898264311428490
- Sands, L. P., Yaffe, K., Covinsky, K., Chren, M. M., Counsell, S., Palmer, R., . . . Landefeld, C. S. (2003). Cognitive screening predicts magnitude of functional recovery from admission to 3 months after discharge in hospitalized elders. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*(1), 37–45.
- Sanders, J. L., Boudreau, R. M., Fried, L. P., Walston, J. D., Harris, T. B., & Newman, A. B. (2011). Measurement of organ structure and function enhances understanding of the physiological basis of frailty: The cardiovascular health study. *Journal of the American Geriatrics Society*, *59*(9), 1581–1588. doi:10.1111/j.1532-5415.2011.03557.x
- Santos-Eggimann, B., Cuénoud, P., Spagnoli, J., & Junod, J. (2009). Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries.

*Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 64(6), 675–681.

- Sarkisian, C. A., Gruenewald, T. L., Boscardin, W. J., & Seeman, T. E. (2008). Preliminary evidence for subdimensions of geriatric frailty: The MacArthur study of successful aging. *Journal of the American Geriatrics Society*, 56(12), 2292–2297.
- Sarkisian, C. A., & Lachs, M. S. (1996). “Failure to thrive” in older adults. *Annals of Internal Medicine*, 124(12), 1072–1078.
- Sawatzky, R., Liu-Ambrose, T., Miller, W. C., & Marra, C. A. (2007). Physical activity as a mediator of the impact of chronic conditions on quality of life in older adults. *Health and Quality of Life Outcomes*, 5(68), 1–11. doi:10.1186/1477-7525-5-68
- Schaap, L. A., Pluijm, S. M., Deeg, D. J., Harris, T. B., Kritchevsky, S. B., Newman, A. B., . . . Visser, M.; Health ABC Study. (2009). Higher inflammatory marker levels in older persons: Associations with 5-year change in muscle mass and muscle strength. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 64(11), 1183–9. doi:10.1093/gerona/glp097
- Schmaltz, H. N., Fried, L. P., Xue, Q. L., Walston, J., Leng, S. X., & Semba, R. D. (2005). Chronic cytomegalovirus infection and inflammation are associated with prevalent frailty in community-dwelling older women. *Journal of the American Geriatrics Society*, 53(5), 747–754.
- Schoevaerds, D., Bietlot, S., Malhomme, B., Rezette, C., Gillet, J. B., Vanpee, D., . . . Swine, C. (2004). Early identification of the geriatric profile in the emergency department: Presentation of the short emergency geriatric assessment (SEGA). *Revue de Geriatrie*, 29(3), 169–178.
- Schrager, M. A., Metter, E. J., Simonsick, E., Ble, A., Bandinelli, S., Lauretani, F., & Ferrucci, L. (2007). Sarcopenic obesity and inflammation in the InCHIANTI study. *Journal of Applied Physiology*, 102(3), 919–925.
- Schulkin, J. (2003). Allostasis: A neural behavioral perspective. *Hormones and Behavior*, 43(1), 21–27.
- Schultz, R., & Williamson G. M. (1993). Psychosocial and behavioral dimensions of physical frailty. *Journals of Gerontology*, 48(Special Issue), 39–43.
- Schultz-Larsen, K., & Avlund, K. (2006). Tiredness in daily activities: A subjective measure for the identification of frailty among non-disabled community-living

- older adults. *Archives of Gerontology and Geriatrics*, 44(1), 83–93.  
doi:10.1016/j.archger.2006.03.005
- Schwab, W. S. (2008). Geriatric syndromes. *Journal of the American Geriatrics Society*, 56(2), 363–364.
- Schwartz, J., & Weiss, S. T. (1993). Peripheral blood leukocyte count and respiratory symptoms. *Annals of Epidemiology*, 3(1), 57–63.  
doi:10.1016/1047-2797(93)90010-2
- Seely, A. J., & Christou, N. V. (2000). Multiple organ dysfunction syndrome: Exploring the paradigm of complex nonlinear systems. *Critical Medicine*, 28(7), 2193–2200.
- Seeman, T., Dubin, L., Seeman, M. (2003). Religiosity, spirituality and health: A critical review of the evidence for biologic pathways. *American Psychology*, 58(1), 53–63.
- Seeman, T., Merkin, S. S., Crimmins, E., Koretz, B., Charete, S., & Karlamangla, A. (2007). Education, income, and ethnic differences in cumulative biologic risk profiles in a national sample of U.S. adults: NHANES III (1988–1994). *Social Science & Medicine*, 66(1), 72–87.
- Seeman, T. E. (1996). Social ties and health: The benefits of social integration. *Annals of Epidemiology*, 6(5), 442–451.
- Seeman, T. E. (2000). Health promoting effects of friends and family on health outcomes in older adults. *American Journal of Health Promotion*, 14(6), 362–370.
- Seeman, T. E., & Crimmins, E. (2001). Social environment effects on health and aging: integrating epidemiologic and demographic approaches and perspectives. *Annals of the New York Academy of Science*, 954, 88–117.
- Seeman, T. E., Guralnik, J. M., Kaplan, G. A., Knudson, L., & Cohen, R. (1989). The health consequences of multiple morbidity in the elderly. The alameda county study. *Journal of Aging & Health*, 1(1), 50–66.
- Seeman, T. E., Lusignolo, T. M., Albert, M., & Berkman, L. (2001). Social relationships, social support, and patterns of cognitive aging in healthy, high-functioning older adults: MacArthur studies of successful aging. *Health Psychology*, 20(4), 243–255.
- Seeman, T. E., & McEwen, B. S. (1996). Impact of social environment characteristics on neuroendocrine regulation. *Psychosomatic Medicine*, 58(5), 459–471.

- Seeman, T. E., Merkin, S. S., Crimmins, E. M., & Karlamangla, A. S. (2010). Disability trends among older Americans: National health and nutrition examination surveys, 1988-Care 1994 and 1999–2004. *American Journal of Public Health, 100*(1), 100–107.
- Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation: Allostatic load and its health consequences. MacArthur studies of successful aging. *Archives of Internal Medicine, 157*(19), 2259–2268.
- Selye, H. (1955). Stress and disease. *Science, 122*(3171), 625–631.
- Selye, H. (1974). *Stress without distress*. Philadelphia, PA: Lippincott.
- Selye, H. (1983). *The stress of life*. New York, NY: McGraw-Hill, Inc.
- Semba, R. D., Bartali, B., Zhou, J., Blaum, C., Ko, C. W., & Fried, L. P. (2006). Low serum micronutrient concentrations predict frailty among older women living in the community. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 61*(5), 594–549.
- Semba, R. D., Guralnik, J. M., Chaves, P., Ricks, M. O., & Fried, L. P. (2004). Iron status and anemia in a population-based study of women with and without disability living in the community: The Women's Health and Aging Studies. *Haematologica, 89*(3), 357–358.
- Shapiro, E., & Tate, R. (1985). Predictors of long-term care facility use among the elderly. *Canadian Journal on Aging, 4*, 11–19.
- Shapiro, E., & Tate, R. (1988). Who is really at risk of institutionalization? *Gerontologist, 28*, 237–245.
- Shega, J. W., Dale, W., Andrew, M., Paice, J., Rockwood, K., & Weiner, D. K. (2012). Persistent pain and frailty: A case for homeostenosis. *Journal of the American Geriatrics Society, 60*(1), 1–5. doi:10.1111/j.1532-5415.2011.03769.x
- Shi, J., Song, X., Yu, P., Tang, Z., Mitnitski, A., Fang, X., & Rockwood, K. (2011). Analysis of frailty and survival from late middle age in the Beijing longitudinal study of aging. *BMC Geriatrics, 11*, 17. doi:10.1186/1471-2318-11-17
- Shore, W. S., & DeLateur, B. J. (2007). Prevention and treatment of frailty in the postmenopausal woman. *Physical Medicine and Rehabilitation Clinics of North America, 18*(3), 609–621, xii.

- Siddiqi, N., Stockdale, R., Britton, A. M., & Holmes, J. (2007). Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev.*, 2007(2), CD005563.
- Silvestri, A., Vitale, C., Ferretti F., Onorati, D., Fini, M., & Rosano, G. M. (2004). Plasma levels of inflammatory c-reactive protein and interleukin-6 predict outcome in elderly patients with stroke. *Journal of the American Geriatrics Society*, 52(9), 1586–1587.
- Simonsick, E. M., Kasper, J. D., & Phillips, C. L. (1998). Physical disability and social interaction: Factors associated with low social contact and home confinement in disabled older women (The Women's Health and Aging Study). *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, 53(4), S209–S217.
- Singh, M., Alexander, K., Roger, V.L., Rihal, C.S., Whitson, H.E., Lerman, A., ...Nair, K.S. (2008). Frailty and its potential relevance to cardiovascular care. *Mayo Clinic Proceedings*, 83(10), 1146–1153.
- Sipe, J. D. (1995). Acute phase proteins in osteoarthritis. *Seminars in Arthritis and Rheumatology*, 25(2), 75–86. doi.org/10.1016/S0049-0172(95)80020-4
- Slaets, J. P. (2006). Vulnerability in the elderly: Frailty. *Medical Clinics of North America*, 90(4), 593–601.
- Song, X., Mitnitski, A., & Rockwood, K. (2010). Prevalence and 10-Year outcomes of frailty in older adults in relation to deficit accumulation. *Journal of the American Geriatrics Society*, 58(4), 681–687. doi:10.1111/j. 1532-5415. 2010. 02764.x
- Song, X., Mitnitski, A., & Rockwood, K. (2011). Nontraditional risk factors combine to predict Alzheimer disease and dementia. *Neurology*, 77(3), 227–234. doi:10.1212/WNL. 0b013e318225c6bc
- Sonnenblick, M., Raveh, D., Gratch, L., & Yinnon, A. (2007). Clinical and demographic characteristics of elderly patients hospitalised in an internal medicine department in Israel. *International Journal of Clinical Practice*, 61(2), 247–254.
- Sorace, J., Won, H. H., Worrall, C., Kelman, J., Saneinejad, S., & MaCurdy, T. (2011). The complexity of disease combinations in the medicare population. *Population Health Management*, 14(4), 161–166.
- Sourial, N., Wolfson, C., Bergman, H., Zhu, B., Karunanathan, S., Quail, J., & Béland, F. (2010). A correspondence analysis revealed frailty deficits aggregate and are multidimensional. *Journal of Clinical Epidemiology*, 63(6), 647–654.

- Speechley, M., & Tinetti, M. (1991). Falls and injuries in frailty and vigorous community elderly persons. *Journal of the American Geriatrics Society*, 39(1), 46–52.
- Speciale, S., Turco, R., Magnifico, F., Bellelli, G., & Trabucchi, M. (2004). Frailty is the main predictor of falls in elderly patients undergoing rehabilitation training. *Age & Ageing*, 33(1), 84–85.
- Stenholm, S., Harris, T. B., Rantanen, T., Visser, M., Kritchevsky, S. B., & Ferrucci, L. (2008). Sarcopenic obesity-definition, etiology and consequences. *Current Opinion in Clinical Nutrition and Metabolic Care*, 11(6), 693–700. doi:10.1097/MCO.0b013e328312c37d
- Sterling, P. (2004). Principles of allostasis: Optimal design, predictive regulation, pathophysiology and rational therapeutics. In J. Schulkin (Ed.), *Allostasis, homeostasis, and the cost of physiologic adaptation* (pp. 17–33). New York, NY: Cambridge University Press.
- Stephens, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain Behavior and Immunity*, 21(7), 901–912.
- Sternberg, S. A., Wershof Schwartz, A., Karunanathan, S., Bergman, H., & Mark Clarfield, A. (2011). The identification of frailty: A systematic literature review. *Journal of the American Geriatrics Society*, 59(11), 2129–2138. doi:10.1111/j.1532-5415.2011.03597.x
- Stephenson, P. H., Wolfe, N. K., Coughlan, R., & Koehn, S. D. (1999). A methodological discourse on gender, independence, and frailty: Applied dimensions of identity construction in old age. *Journal of Aging Studies*, 13(4), 391–401.
- Stewart, J. A. (2006). The detrimental effects of allostasis: Allostatic load as a measure of cumulative stress. *Journals of Physiological Anthropology*, 25(1), 133–145.
- Stiffler, K. A., Finley, A., Midha, S., & Wilber, S. T. (2013). Frailty assessment in the emergency department. *Journal of Emergency Medicine*, pii: S0736-4679(12), 1571–1575. doi:10.1016/j.jemermed.2012.11.047
- Strandberg, T. E., & Pitkälä, K. H. (2007). Frailty in elderly people. *Lancet*, 369(9570), 1328–1329.
- Strawbridge, W. J., Shema, S. J., Balfour, J. L., Higby, H. R., & Kaplan, G. A. (1998). Antecedents of frailty over three decades in an older cohort. *Journals of Gerontology. Series B, Social Sciences and Medical Sciences*, 53(1), S9–S16.

- Studenski, S. A. (2012). Gait speed in hospitalized older people: Comment on “assessing gait speed in acutely ill older patients admitted to an acute care for elders hospital unit.” *Archives of Internal Medicine*, *172*(4), 358–359.
- Studenski, S. (2009). Bradypedia: Is gait speed ready for clinical use? *Journal of Nutrition, Health and Aging*, *13*(10), 878–880.
- Studenski, S., Hayes, R. P., Leibowitz, R. Q., Bode, R., Lavery, L., Walston, J., . . . Perera, S. (2004). Clinical global impression of change in physical frailty: Development of a measure based on clinical judgment. *Journal of the American Geriatrics Society*, *52*(9), 1560–1566.
- Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., . . . Guralnik, J. (2011). Gait speed and survival in older adults. *Journal of the American Medical Association*, *305*(1), 50–58. doi:10.1001/jama.2010.1923
- Sündermann, S. H., Dademasch, A., Praetorius, J., Kempfert, J., Dewey, T., Falk, V., . . . Walther, T. (2011). Comprehensive assessment of frailty for elderly high-risk patients undergoing cardiac surgery. *European Journal of Cardiothoracic Surgery*, *39*(1), 33–37.
- Sündermann, S. H., Dademasch, A., Rastan, J., Rodriguez, H., Mohr, F. W., & Falk, V. (2011). One-year follow-up of patients undergoing elective cardiac surgery assessed with the comprehensive assessment of frailty test and its simplified form. *Interactive Cardiovascular and Thoracic Surgery*, *13*(2), 119–123.
- Sutton, M., Grimmer-Somers, K., & Jeffries, L. (2009). Screening tools to identify hospitalised elderly patients at risk of functional decline: A systematic review. *International Journal of Clinical Practice*, *62*(12), 1900–1909. doi:10.1111/j.1742-1241.2008.01930.x
- Szanton, S. L., Allen, J. K., Seplaki, C. L., Bandeen-Roche, K., & Fried, L. P. (2009). Allostatic load and frailty in the womens health and aging studies. *Biological Research for Nursing*, *10*(3), 248–256.
- Szanton, S. L., Allen, J. K., Thorpe, R. J., Seeman, T., Bandeen-Roche, K., & Fried, L. P. (2008). Effect of financial strain on mortality in community-dwelling older women. *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *63*(6), S369–S374.
- Szanton, S. L., Gill, J. M., & Allen, J. K. (2005). Allostatic load: A mechanism of socioeconomic health disparities? *Biological Research for Nursing*, *7*(1), 7–15.

- Szanton, S. L., Seplaki, C. L., Thorpe, R. J., Allen, J. K., & Fried L. P. (2010). Socioeconomic status is associated with frailty: The women's health and aging studies. *Journal of Epidemiology and Community Health*, *64*(1), 63–67.
- Szanton, S. L., Thorpe, R. J., & Whitfield, K. (2010). Life-course financial strain and health in African-Americans. *Social Science Medicine*, *71*(2), 259–265.
- Taaffe, D. R., Harris, T. B., Ferrucci, L., Rowe, J., & Seeman, T. E. (2000). Cross-sectional and prospective relationships of interleukin-6 and c-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *55*(12), M709–M715.
- Tabachnik, B. G., & Fidell, L. S. (2007). *Using multivariate statistics* (5th ed.). Boston, MA: Pearson.
- Tak, L. M., Bakker, S. J., Slaets, J. P., & Rosmalen, J. G. (2009). Is high-sensitive c-reactive protein a biomarker for functional somatic symptoms? A population-based study. *Brain, Behavior, and Immunity*, *23*, 1014–1019.
- Taylor, S. E., Lehman, B. J., Kiefe, C. I., & Seeman, T. E. (2006). Relationship of early life stress and psychological functioning to adult c-reactive protein in the coronary artery risk development in young adults study. *Biology Psychiatry*, *60*(8), 819–824.
- Tennstedt, S. L., & McKinlay, J. B. (1994). Frailty and its consequences. *Social Science Medicine*, *38*(7), 863–865.
- Terzian, A. S., Holman, S., Nathwani, N., Robison, E., Weber, K., Young, M., . . . Gange, S. J.; Women's Interagency HIV Study. (2009). Factors associated with preclinical disability and frailty among HIV-infected and HIV-uninfected women in the era of cART. *Journal of Women's Health*, *18*(12), 1965–1974. doi:10.1089/jwh.2008.1090
- The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. (2012). American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, *60*(4), 616–631. doi:10.1111/j.1532-5415.2012.03923.x
- The Canadian Study of Health and Aging Working Group. (2001). Disability and frailty among elderly Canadians: A comparison of six surveys. *International Psychogeriatrics*, *13*(Supp. 1), 159–167. doi:10.1017/S1041610202008104

- Theou, O., Jones, G. R., Jakobi, J. M., Mitnitski, A., & Vandervoort, A. A. (2011). A comparison of the relationship of 14 performance-based measures with frailty in older women. *Applied Physiology Nutrition and Metabolism*, 36(6), 928–938.
- Thornlow, D. K., Anderson, R., & Oddone, E. (2009). Cascade iatrogenesis: Factors leading to the development of adverse events in hospitalized older adults. *International Journal of Nursing Studies*, 46(11), 1528–1535. doi:10.1016/j.ijnurstu.2009.06.015
- Tinetti, M. E., Inouye, S. K., Gill, T. M., & Doucette, J. T. (1995). Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. *Journal of the American Medical Association*, 273(17), 1348–1353.
- Topinková, E. (2008). Aging, disability and frailty. *Annals of Nutrition & Metabolism*, 52(Supplement), 6–11. doi:10.1159/000115340
- Toye, C., White, K., & Rooksby, K. (2006). Fatigue in frail elderly people. *International Journal of Palliative Nursing*, 12(5), 202–208.
- Tracy, R. P. (2003). Emerging relationships of inflammation, cardiovascular disease and chronic diseases of aging. *International Journal of Obesity and Related Metabolic Disorders*, 27(Suppl. 3), S29–S34.
- U.S. Census Bureau. (2003). *Population Division, Census 2003*. Retrieved from <http://www.census.gov/popest/>
- U.S. Census Bureau. (2008). *Projections of the population by selected age groups and sex for the United States: 2010 to 2050 (NP2008-T2)*. U.S. Population Projections. Population Division, U.S. Census Bureau. August 14, 2008. Retrieved from <http://www.census.gov/population/www/projections/summarytables.html>
- U.S. Census Bureau. (2012). *U.S. Census Bureau: State and county QuickFacts*. Retrieved from <http://quickfacts.census.gov/qfd/states/37000.html>
- van Gool, C. H., Kempen, G. I., Penninx, B. W., Deeg, D. J., Beekman, A. T., & van Eijk, J. T. (2003). Relationship between changes in depressive symptoms and unhealthy lifestyles in late middle aged and older persons: Results from the longitudinal aging study Amsterdam. *Age & Ageing*, 32(1), 81–87.
- van Iersel, M. B., & Rikkert, M. C. (2006). Frailty criteria give heterogeneous results when applied in clinical practice. *Journal of the American Geriatrics Society*, 54(4), 728–729.

- van Kempen, J. A., Robben, S. H., Zuidema, S. U., Olde Rikkert, M. G., Melis, R. J., & Schers, H. J. (2012). Home visits for frail older people: A qualitative study on the needs and preferences of frail older people and their informal caregivers. *British Journal of General Practice*, *62*(601), e554–560. doi:10.3399/bjgp12X653606
- Vanitallie, T. B. (2003). Frailty in the elderly: Contributions of sarcopenia and visceral protein depletion. *Metabolism*, *52*(10 Suppl. 2), 22–26.
- Vaz Fragoso, C. A., Gahbauer, E. A., Van Ness, P. H., & Gill, T. M. (2009). Sleep–wake disturbances and frailty in community-living older persons. *Journal of the American Geriatrics Society*, *57*(11), 2094–2100.
- Vellas, B., Cestac, P., & Moley, J. E. (2012). Implementing frailty into clinical practice: We cannot wait. *Journal of Nutrition in Health and Aging*, *16*(7), 599–600.
- Verdery, R. B. (1997a). Clinical evaluation of failure to thrive in older people. *Clinical Geriatric Medicine*, *13*, 769–778.
- Verdery, R. B. (1997b). Failure to thrive in old age: Follow-up on a workshop. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *52*, M333–M336.
- Verdery, R. B. (1998). Failure to thrive in older people. *Journal of Nutrition in Health and Aging*, *2*(2), 69–72.
- Verghese, J., Holtzer, R., Oh-Park, M., Derby, C. A., Lipton, R. B., & Wang, C. (2011). Inflammatory markers and gait speed decline in older adults. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *66*(10), 1083–1089. doi:10.1093/gerona/qlr099
- Verghese, J., Wang, C., & Holtzer, R. (2011). Relationship of clinic-based gait speed measurement to limitations in community-based activities in older adults. *Archives of Physical Medicine & Rehabilitation*, *92*(5), 844–846. doi:10.1016/j.apmr.2010.12.030
- Verghese, J., & Xue, X. (2011). Predisability and gait patterns in older adults. *Gait & Posture*, *33*(1), 98–101. doi:10.1016/j.gaitpost.2010.10.004.
- Vermeulen, J., Neyens, J. C., van Rossum, E., Spreuwenberg, M. D., & de Witte, L. P. (2011). Predicting ADL disability in community-dwelling elderly people using physical frailty indicators: A systematic review. *BMC Geriatrics*, *11*(11), 33.

- Villareal, D. T., Banks, M., Sinacore, D. R., Siener, C., & Klein, S. (2006). Effect of weight loss and exercise on frailty in obese older adults. *Archives of Internal Medicine*, *166*(8), 860–866.
- Visser, M. (2011). Obesity, sarcopenia and their functional consequences in old age. *Proceedings of the Nutrition Society*, *70*(1), 114–118.
- Visser, M., Bouter, L. M., McQuillan, G. M., Wener, M. H., & Harris, T. B. (1999). Elevated c-reactive protein levels in overweight and obese adults. *Journal of the American Medical Association*, *282*(22), 2131–135.
- Visser, M., Kritchevsky, S. B., Newman, A. B., Goodpaster, B. H., Tylavsky, F. A., Nevitt, M. C., & Harris, T. B.; Health, Aging and Body Composition Study. (2005). Lower serum albumin concentration and change in muscle mass: The health, aging and body composition study. *American Journal of Clinical Nutrition*, *82*(3), 531–537.
- Vitagliano, G., Curtis, J. P., Concato, J., Feinstein, A. R., Radford, M. J., & Krumholz, H. M. (2004). Association between functional status and use and effectiveness of beta-blocker prophylaxis in elderly survivors of acute myocardial infarction. *Journal of the American Geriatrics Society*, *52*(4), 495–501.
- von Känel, R., Dimsdale, J. E., Mills, P. J., Ancoli-Israel, S., Patterson, T. L., Mausbach T., & Grant, I. (2006). Effect of alzheimer caregiving stress and age on frailty markers interleukin-6, c-reactive protein, and d-dimer. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *61*(9), 963–969.
- Walke, L. M., Gallo, W. T., Tinetti, M. E., & Fried, T. R. (2004). The burden of symptoms among community-dwelling older persons with advanced chronic disease. *Archives of Internal Medicine*, *164*(21), 2321–2324.
- Walker, C., Hogstel, M. O., & Curry, L. C. (2007). Hospital discharge of older adults. How nurses can ease the transition. *American Journal of Nursing*, *107*(6), 60–71.
- Walston, J., & Fried, L. P. (1999). Frailty and the older man. *Medical Clinics of North America*, *83*(5), 1173–1194.
- Walston, J., Hadley, E. C., Ferrucci, L., Guralnik, J. M., Newman, A. B., Studenski, S. A., . . . Fried, L. P. (2006). Research agenda for frailty in older adults: Toward a better understanding of physiology and etiology. Summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *Journal of the American Geriatrics Society*, *54*(6), 991–1001.

- Walston, J., McBurnie, M. A., Newman, A., Tracy, R. P., Willem, J., Kop, W. J., . . . Fried, L. P. (2002). Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: Results from the cardiovascular health study. *Archives of Internal Medicine*, *162*(20), 2333–2341. doi:10-1001/pubs.Arch Intern Med
- Walther, C., Möbius-Winkler, S., Linke, A., Bruegel, M., Thiery, J., Schuler, G., & Halbrecht, R. (2008). Regular exercise training compared with percutaneous intervention leads to a reduction of inflammatory markers and cardiovascular events in patients with coronary artery disease. *European Journal of Cardiovascular Prevention and Rehabilitation*, *15*(1), 107–112.
- Weber, L., & Fore, E. (2007). Race, ethnicity, and health: An intersectional approach. In J. Feagin & H. Vera (Eds.), *Handbook of the Sociology of Racial and Ethnic Relations* (pp. 191–218). New York, NY: Springer.
- Weiss, C. O. (2011). Frailty and chronic diseases in older adults. *Clinics in Geriatric Medicine*, *27*(1), 39–52.
- Weiss, C. O., Hoenig, H. H., Varadhan, R., Simonsick, E. M., & Fried, L. P. (2010). Relationships of cardiac, pulmonary, and muscle reserves and frailty to exercise capacity in older women. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *65*(3), 287–294.
- Whitson, H., Purser, J. L., & Cohen, H. J. (2007). Frailty thy name is . . . Phrailty? *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *62*(7), 728–730.
- Whitson, H. E., Ansah, D., Whitaker, D., Potter, G., Cousins, S. W., MacDonald, H., . . . Cohen, H. J. (2010). Prevalence and patterns of comorbid cognitive impairment in low vision rehabilitation for macular disease. *Archives of Gerontology and Geriatrics*, *50*(2), 209–212.
- Whitson, H. E., Hastings, S. N., Landerman, L. R., Fillenbaum, G. G., Cohen, H. J., & Johnson, K. S. (2011). Black-white disparity in disability: The role of medical conditions. *Journal of the American Geriatrics Society*, *59*(5), 844–850. doi:10.1111/j.1532-5415.2011.03401.x
- Whitson, H. E., Landerman, L. R., Newman, A. B., Fried, L. P., Pieper, C. F., & Cohen, H. J. (2010). Chronic medical conditions and the sex-based disparity in disability: The cardiovascular health study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *65*(12), 1325–1331.

- Whitson, H. E., Sanders, L. L., Pieper, C. F., Morey, M. C., Oddone, E. Z., Gold, D. T., & Cohen, H. J. (2009). Correlation between symptoms and function in older adults with comorbidity. *Journal of the American Geriatrics Society*, *57*(4), 676–682.
- Wieland, D., & Hirth, V. (2003). Comprehensive geriatric assessment. *Cancer Control*, *10*(6), 454–462.
- Wikby, A., Ferguson, F., Forsey, R., Thompson, J., Strindhall, J., Löfgren, . . . Johansson, B. J. (2005). An immune risk phenotype, cognitive impairment, and survival in very late life: Impact of allostatic load in Swedish octogenarian and nonagenarian humans. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *60*(5), 556–565.
- Wilhelm-Leen, E. R., Hall, Y. N., Tamura, M. K., & Chertow, G. M. (2009). Frailty and chronic kidney disease: The third national health and nutrition evaluation survey. *American Journal of Medicine*, *122*(7), 664–671.
- Williams, E. I., & Fitton, F. (1988). Factors affecting early unplanned readmission of elderly patients to hospital. *BMJ*, *297*(6651), 784–787.
- Williams, R. C. Jr., Harmon, M. E., Burlingame, R., & Du Clos, T. W. (2005). Studies of serum c-reactive protein in systemic lupus erythematosus. *The Journal of Rheumatology*, *32*(3), 454–461.
- Windgassen, E. B., Funtowicz, L., Lunsford, T. N., Harris, L. A., & Mulvagh, S. L. (2011). C-reactive protein and high-sensitivity c-reactive protein: An update for clinicians. *Postgraduate Medicine*, *123*(1), 114–119.  
doi:10.3810/pgm.2011.01.2252
- Winograd, C. H., Gerety, M. B., Brown, E., & Kolodny, V. (1988). Targeting the hospitalized elderly for geriatric consultation. *Journal of the American Geriatric Society*, *36*(12), 1113–1119.
- Winograd, C. H., Gerety, M. B., Chung, M., Goldstein, M. K., Dominguez, F., & Vallone, R. (1991). Screening for frailty: Criteria and predictors of outcomes. *Journal of the American Geriatrics Society*, *39*(8), 778–784.
- Wittink, M. N., Joo, J. H., Lewis, L. M., & Barg, F. K. (2009). Losing faith and using faith: Older Americans discuss spirituality, religious activities, and depression. *Society of General Internal Medicine*, *24*(3), 402–407.
- Woo, J., Goggins, W., Sham, A., & Ho, S. C. (2005). Social determinants of frailty. *Gerontology*, *51*(6), 402–408.

- Woo, J., Goggins, W., Sham, A., & Ho, S. C. (2006). Public health significance of the frailty index. *Disability and Rehabilitation*, 28(8), 515–521.
- Woo, J., Leung, J., & Morley, J. E. (2012). Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. *Journal of the American Geriatrics Society*, 60(8), 1478–1486. doi: 10.1111/j.1532-5415.2012.04074.x
- Woo, K. (2000). Physical activity as a mediator between dyspnea and fatigue in patients with chronic obstructive pulmonary disease. *Canadian Journal of Nursing Research*, 32(3), 85–98.
- Woodhouse, K. W., & O'Mahony, M. S. (1997). Frailty and aging. *Age and Ageing*, 26(4), 245–246.
- Woodhouse, K. W., Wynne, H., Baillie, S., James, O. F., & Rawlins, M. D. (1988). Who are the frail elderly? *Quarterly Journal of Medicine*, 68(255), 505–506.
- Wolff, J. L., & Kasper, J. D. (2006). Caregivers of frail elders: Updating a national profile. *Gerontologist*, 46(3), 344–356.
- Woolley, D. C. (2004). How useful is the concept of 'failure to thrive' in care of the aged? *American Family Physician*, 70(2), 248, 257.
- World Health Organization (WHO). (2006). *Global database for body mass index. BMI Classification*. Retrieved from [http://apps.who.int/bmi/index.jsp?introPage=intro\\_3.html](http://apps.who.int/bmi/index.jsp?introPage=intro_3.html)
- Xue, Q. L. (2011). The frailty syndrome: Definition and natural history. *Clinics in Geriatric Medicine*, 27(1), 1–15.
- Xue, Q. L., Bandeen-Roche, K., Varadhan, R., Zhou, J., & Fried, L. P. (2008). Initial manifestations of frailty criteria and the development of frailty phenotype in the women's health and aging study II. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 63(9), 984–990.
- Xue, Q. L., Walston, J. D., Fried, L. P., & Beamer, B. A. (2011). Prediction of risk of falling, physical disability, and frailty by rate of decline in grip strength: The women's health and aging study. *Archives of Internal Medicine*, 171(12), 1119–1121. doi:10.1001/archinternmed.2011.252
- Yach, D., Hawkes, C., Gould, C. L., & Hofman, K. J. (2004). The global burden of chronic diseases: Overcoming impediments to prevention and control. *Journal of the American Medical Association*, 291(21), 2616–2622.

- Yang, Y., & Lee, L. C. (2010). Dynamics and heterogeneity in the process of human frailty and aging: Evidence from the U.S. older adult population. *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, 65(2), 46–55.
- Yao, X., Li, H., & Leng, S. X. (2011). Inflammation and immune system alterations in frailty. *Clinics in Geriatric Medicine*, 27(1), 79–87.
- Yassuda, M. S., Lopes, A., Cachioni, M., Falcao, D. V., Batistoni, S. S., Guimaraes, V. V., & Neri, A. L. (2012). Frailty criteria and cognitive performance are related: Data from the FIBRA study in Ermelino Matarazzo, São Paulo, Brazil. *Journal of Nutrition in Health & Aging*, 6(1), 55–61.
- Yip, A. M., Gorman, M. C., Stadnyk, K., Mills, W. G., MacPherson, K. M., & Rockwood, K. (1998). A standardized menu for goal attainment scaling in the care of frail elders. *Gerontologist*, 38(6), 735–742.
- Yorgason, J. B., Booth, D., & Johnson, D. (2008). Health, disability and marital quality. Is the association different for younger versus older cohorts? *Research on Aging*, 30(6), 623–648.
- Yoshida, Y., Iwasa, H., Kumagai, S., Yoshida, H., & Suzuki, T. (2010). Association between c-reactive protein (CRP) level and physical performance in community-dwelling elderly in Japan. *Archives of Gerontology and Geriatrics*, 51(2), 164–168.
- Young, Y., Frick, K. D., & Phelan, E. A. (2009). Can successful aging and chronic illness coexist in the same individual? A multidimensional concept of successful aging. *Journal of the American Medical Directors Association*, 10(2), 87–92.
- Zakai, N. A., Katz, R., Hirsch, C., Shlipak, M. G., Chaves, P. H., Newman, A. B., & Cushman, M. (2005). A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: The cardiovascular health study. *Archives of Internal Medicine*, 165(19), 2214–2220.
- Zalon, M. L. (2004). Correlates of recovery among older adults after major abdominal surgery. *Nursing Research*, 53(2), 99–106.
- Zisberg, A., Shadmi, E., Sinoff, G., Gur-Yaish, N., Srulovici, E., & Admi, H. (2011). Low mobility during hospitalization and functional decline in older adults. *Journal of the American Geriatrics Society*, 59(2), 266–273.  
doi:10.1111/j.1532-5415.2010.03276.x

Zittel, K. M., Lawrence, S., & Wodarski, J. S. (2002). Biopsychosocial model of health and healing: Implications for health social work practice. *Journal of Human Behavior in Social Environment*, 5(1), 19–29.