

BARELLA, LISA A., Ph.D. The Relationship of Physical Activity and Aerobic Fitness with Health-Related Quality of Life and Executive Function in Celiac Disease Patients. (2008)

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Celiac Disease (CD) is a multisystem disorder that is caused by gluten and affects approximately 1% of the United States population. Approximately 10% of CD patients have neurological complications, such as ataxia, brain atrophy, dementia, epileptic seizures, peripheral neuropathy, and cognitive impairment. CD patients have also been found to have lower health-related quality of life (HRQL) than the general population. Given the established relationships of physical activity and aerobic fitness with HRQL and executive function in other chronic disease populations and in older adults, it seems likely that these same relationships may exist for CD patients. However, these relationships have not been investigated. Therefore, the purpose of this study was to determine if both physical activity (number of vigorous bouts of physical activity/week; MET hours/week) and aerobic fitness were positive predictors of HRQL and executive function in CD patients. The relationship of functional fitness with those same outcome variables was also explored given the established positive relationship between functional fitness and HRQL. Separate canonical correlations were used for the HRQL composite and the executive function composite with the physical activity measures, aerobic fitness, and functional fitness. Canonical correlations for the HRQL composite with number of vigorous bouts of physical activity/week, MET hours/week, aerobic fitness, or functional fitness were not statically significant. However, canonical correlations for the executive function composite with number of vigorous bouts of physical activity/week ( $R_c = .55$ ;

$p=0.02$ ) and functional fitness ( $R_c = .57; p=0.01$ ) were statistically significant. The results do not support positive relationships for any of the predictor variables with HRQL, and this may be due to our high functioning CD sample, which scored higher than normative scores on measures of HRQL. However, these findings do support a positive relationship for number of vigorous bouts of physical activity/week and functional fitness with executive function.

THE RELATIONSHIP OF PHYSICAL ACTIVITY AND AEROBIC FITNESS WITH  
HEALTH-RELATED QUALITY OF LIFE AND EXECUTIVE  
FUNCTION IN CELIAC DISEASE PATIENTS

by

Lisa A. Barella

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Approved by

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Committee Chair

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“To my parents, Henry and Linda Barella, for their continued support of  
my education and professional career goals”

APPROVAL PAGE

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

Committee Chair \_\_\_\_\_

Committee Members \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_  
Date of Acceptance by Committee

\_\_\_\_\_  
Date of Final Oral Examination

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## PREFACE

Celiac Disease (CD) is a greatly undiagnosed hereditary autoimmune disorder. Four of my immediate family members have CD and the process of diagnosis for many of us was enduring. When I was diagnosed and began researching the topic in 2003, I noticed the lack of research addressing mental health and health-related quality of life (HRQL) in those with CD, as well as a lack of awareness in the community about the disease and the gluten free diet. I continued reading peer-reviewed articles on many CD related topics and while in graduate school developed a passion for studying how physical activity was related to HRQL and executive function. Further readings of research on medical pathologies and neurology in CD patients, encouraged me to develop hypotheses about what was occurring with HRQL and executive function in CD patients. There was no research exploring the potential benefits of physical activity, a behavior that has been linked to positive mental and physical health in adult populations, older adults, and many chronic disease populations. Therefore, this current research was developed to fill a gap in both the CD and physical activity literature, while also supporting areas of research that I am truly committed to.

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## CHAPTER I

### INTRODUCTION

Celiac Disease (CD) is a multisystem disorder that is caused by gluten and affects approximately 1% of the United States population (Dubé et al., 2005). CD is greatly underdiagnosed and is the most common hereditary autoimmune disorder in the U.S. (Green & Jones, 2006). In samples with CD that responded to surveys or when biopsy CD disease patients were assessed, two to three times as many adult women as adult men were found to have CD (Green, 2005; Green et al., 2001). CD is associated with neurological complications, such as ataxia, brain atrophy, dementia, epileptic seizures, and peripheral neuropathy (Green & Jones, 2006; Hu, Murray, Greenaway, Parisi, & Josephs, 2006; Kieslich et al., 2001; Vaknin, Eliakim, Ackerman, & Steiner, 2004) and cognitive impairment (Burk et al., 2001). Further, there is an association with increased depression (Addolorato et al., 2001), anxiety (Addolorato et al., 2001), and fatigue (Siniscalchi et al., 2005). Low levels of quality of life (QoL) (Hallert et al., 2002; Hallert et al., 1998) and low levels of health-related quality of life (Häuser, Gold, Caspary, & Stallmach, 2006; Häuser, Stallmach, Caspary, & Stein, 2007) have also been associated with CD.

QoL, health related quality of life (HRQL), and cognition, specifically executive function, are particularly important outcome variables to target when treating CD patients. CD patients have been found to have lower HRQL than the general population (Häuser et al., 2006) yet HRQL is an important consideration for CD patients due to their

need for lifelong adherence to the gluten-free (GF) diet and the complications of having a chronic disease. In fact, the National Institute of Health now mandates that any study that assesses gastrointestinal (GI) disease, such as CD, must also assess HRQL.

In addition to hampered HRQL, approximately 10% of CD patients have neurological complications (Addolorato et al., 2004; Ghezzi & Zaffaroni, 2001; Holmes, 1997) which occur in both child and adult onset CD. Neurological symptoms include neuropathy (Kaplan et al., 1988), ataxia (Cooke & Smith, 1966), brain atrophy (Hu, Murray, Greenaway, Parisi, & Josephs, 2006), epilepsy (Holmes, 1997), and dementia (Hu et al., 2006). Further, CD patients have been found to have neurological deficiencies in brain regions associated with executive functioning. Deterioration of the cerebellum, brainstem, spinal cord, and deep gray matter (Beyenburg, Scheid, Deckert-Schluter, & Lagreze, 1998; Kinney, Burger, Hurwitz, Hijmans, & Grant, 1982) has been found in CD patients, along with lesions within the white matter of the brainstem, cerebellum, and cerebrum (Ghezzi, Filippi, Falini, & Zaffaroni, 1997). Focal, diffused, or nonspecific frontal lobe changes and dense basal ganglia calcifications have also been found in CD patients (Hu et al., 2006). Finally, lower cerebral perfusion in the frontal and parietal lobes has been found in CD patients (Addolorato et al., 2004).

Although there have been numerous studies conducted on the physiology of these neurological complications using magnetic resonance imaging, research investigating cognitive performance and behavioral implications as a result of these neurological deficiencies in CD patients is limited. In fact, there are only three articles to date that have employed cognitive performance tests. Hallert and Astrom (1983) demonstrated no

cognitive impairment in adult CD patients when neurological test scores were compared to those of the general population. However, Burk et al. (2001) found significant differences in executive function in those with cerebral ataxia who also had gluten sensitivity compared to healthy controls. Hu et al. (2006) showed global cognitive impairment, memory deficits, and learning inefficiency in five CD patients compared to normative data. The mixed findings and the extremely limited cognitive behavioral research in CD patients suggest that further research is warranted.

Currently, most of the CD-related QoL/HRQL and neurological research has focused on the impact of the gluten free (GF) diet. The results have been mixed in that some research has found that CD patients currently adhering to the GF diet were not different, in terms of reported QoL, from healthy controls (Viljamaa et al., 2005); however, other research has found that the GF diet is at times able to improve HRQL, but not to the level of the general population (Häuser et al., 2006). Further, the GF diet has not been found to impact the progression of neurological complications. Therefore, knowing that the GF diet may not be able to normalize HRQL in CD patients, or affect the progression of neurological diseases, other behavioral approaches that have been shown to impact HRQL and cognition should be investigated in CD populations. Specifically, the potential influence of physical activity and aerobic fitness on HRQL and cognitive performance in CD patients should be explored.

There are established relationships between physical activity and QoL in older adults (Courneya & Friedenreich, 1999; Rejeski & Mihalko, 2001) and chronic disease populations (Courneya & Friedenreich, 1999; Katula, Blissmer, & McAuley, 1999;

Mannerkorpi, Nyberg, Ahlmen, & Ekdahl, 2000). Further, there are numerous studies that assess the impact of physical activity in other populations and these studies have been meta-analytically reviewed for elderly persons with cognitive impairment (Heyn, Abreu, & Ottenbacher, 2004), healthy and sedentary older adults (Colcombe et al., 2003), children (Sibley & Etnier, 2003) and across all ages (Etnier, Nowell, Landers, & Sibley, 2006; Etnier et al., 1997). These meta-analyses consistently show that chronic physical activity positively impacts cognitive performance.

Despite the large body of literature demonstrating positive relationships between chronic physical activity and psychological outcomes in healthy populations and in a variety of chronic illnesses, these relationships between physical activity and HRQL in people with CD have only been explored once in a preliminary pilot. HRQL and satisfaction with life (SWL) were investigated in CD patients as part of a preliminary study, which was split into 2 phases. In Phase 1, there was a statistically significant correlation ( $r=.70$ ) between bouts of vigorous physical activity and the HRQL composite. In Phase 2, moderate positive correlations were found for  $VO_2$  peak with the SF-36 aggregate physical component score. MET hours per week did not strongly predict HRQL or SWL in either phase. The findings from Phase 1 are encouraging and additional survey research is needed to clarify the relationships found and further explore the measures of physical activity. The small sample in Phase 2 does not allow strong conclusions to be drawn, but does provide us with exploratory evidence of the relationships between  $VO_2$  peak and HRQL.

This pilot study data illustrates the need to determine if physical activity and aerobic fitness are related to HRQL and cognitive performance in daily life for CD patients. First, correlational studies will be needed to determine if a relationship exists and the strength of that relationship. Once this is determined, causal studies can be developed to determine the effect of physical activity and the optimal dose. Physical activity has not been explored as a potential behavioral treatment in CD patients, yet based upon past research with other populations, physical activity clearly has the potential to improve both HRQL and cognitive performance. This gap in the literature has led me to propose assessing both HRQL and executive function in CD patients through a correlational design, as it is critical to find a behavioral tool, such as physical activity, that might be beneficial for these impaired areas in CD patients.

Therefore, the overall objective of this research is to identify the degree to which physical activity and aerobic fitness predict HRQL and cognitive function in CD patients. The primary hypothesis is that both higher self-reported physical activity and higher aerobic fitness will significantly predict higher HRQL in CD patients. The secondary goal is to determine the relationship between physical activity, aerobic fitness and cognitive function in CD patients. I hypothesize that both higher self-reported physical activity and higher aerobic fitness will significantly predict better cognitive function in CD patients. Finally, the relationship between functional fitness, executive function, and HRQL will also be investigated on an exploratory basis.

The specific aims are as follows:

Specific Aim #1 is to identify the degree to which self-reported physical activity (MET hours per week; number of bouts of vigorous physical activity) and aerobic fitness predict HRQL in CD patients.

Specific Aim #2 is to identify the degree to which self-reported physical activity (MET hours per week; number of bouts of vigorous physical activity) and aerobic fitness predict executive function in CD patients.

The exploratory aim is designed to investigate the relationship between functional fitness, as measured by the Timed Up and Go Test (TUG), and HRQL and executive function in CD patients.

## CHAPTER II

### REVIEW OF THE LITERATURE

#### *Introduction*

It is believed that Celiac Disease (CD) affects 1% of the U.S. population and it is estimated that 97% of these people are currently undiagnosed (Green & Jones, 2006). In CD research, two to three times as many adult women have CD as adult men; however, after 65 years of age, the number of women with CD is more similar to the number of men with CD (Green et al., 2001). Not only is CD greatly underdiagnosed, but the average time to diagnosis is approximately 9 years (Green & Jones, 2006). Further, it is now recognized as the most common hereditary autoimmune disease in the U.S. (Green & Jones, 2006). Neurological complications (Hu et al., 2006; Kieslich et al., 2001; Vaknin et al., 2004) have been found to be associated with CD. Further, increased depression (Addolorato et al., 2001), anxiety (Addolorato et al., 2001), and heightened fatigue (Siniscalchi et al., 2005) have been found in those with CD. Low levels of quality of life (Hallert et al., 2002; Hallert et al., 1998), and low levels of health related quality of life (Häuser et al., 2006; Häuser et al., 2007) are also present in some CD patients.

In fact, at the NIH Consensus Statement on CD (2004), it was stated that researchers should “investigate the quality of life in individuals with CD”. The term quality of life (QoL) encompasses many aspects of one’s overall well-being, including mental, physical, social, and cognitive aspects. Further, maintaining cognitive abilities

throughout one's lifetime is important as cognitive performance has implications for individuals in the workforce, relationships, and overall QoL.

Physical activity is a behavior that may be important for psychological health, QoL, and cognitive performance. There are established relationships between physical activity and health-related quality of life (HRQL) or QoL in older adults (Courneya & Friedenreich, 1999; Rejeski & Mihalko, 2001) and chronic disease populations (Courneya & Friedenreich, 1999; Katula, Rejeski, Wickley, & Berry, 2004; Mannerkorpi et al., 2000). Physical activity consistently has been shown to have a positive influence on QoL in older adults (Elavsky et al., 2005). In other populations, acute exercise (Brisswalter, Arcelin, Audiffren, & Delignieres, 1997; Etnier et al., 1997; Tomporowski, 2003) and chronic exercise (Colcombe & Kramer, 2003; Etnier et al., 1997) have been shown to positively impact cognitive performance; however, this relationship has not been tested in CD patients.

Given the research indications that higher physical activity levels are associated with improved HRQL and cognitive functioning in the general population and in certain disease populations, it seems plausible that physical activity, and possibly aerobic fitness, may be positively associated with HRQL and cognitive performance in CD patients. These questions have not been addressed with CD patients.

### *Celiac Disease*

#### *Overview*

CD is a multi-symptom disorder that is caused by gluten sensitivity, which affects approximately 1% of the United States population (Dubé et al., 2005). In a survey

administered to CD support groups in the United States more women than men responded to having CD (2.9:1); however, in those over 65 years of age, the number of females is more similar to the number of males (Green et al., 2001). Also, when biopsy diagnosed CD patients were assessed at the Celiac Center at Columbia University, the ratio of women to men was 1.7 to 1.0 (Green, 2005). In the Italian population, the percentage of female study participants with CD was slightly higher than the percentage of male study participants (52.1% vs. 47.9%) (Volta et al., 2001).

CD was originally called Celiac Sprue. In people with CD, the attempt to digest gluten, the major protein component of wheat, triggers an immune response. Immune responses cause inflammation and villous atrophy (flattening or shrinking of the villi) in the small intestine. As a result of this inflammation and flattening of the villi, negative symptoms begin to occur. These symptoms of CD include malabsorption, dental enamel defects, fatty stools, amenorrhea and delayed puberty, diarrhea, distended stomach, vomiting, fatigue, and failure to thrive (in some CD patients) (Alaedini & Green, 2005). If GI symptoms are lacking, then CD patients are classified as having “asymptomatic”, “atypical” or “silent” CD (Green & Jabri, 2006). Additional complications include insulin-dependent diabetes mellitus, lymphoma, iron-deficiency anemia, thyroid disease (Carta et al., 2002) and osteoporosis (Green & Jabri, 2006). For example, insulin dependent diabetes mellitus in CD patients has been reported to be 8-10% (Green & Jabri, 2006), where the prevalence in non-CD patients is 7.8% (National Institute of Diabetes and Digestive and Kidney Diseases, 2008). Other autoimmune diseases have been found to occur three to ten times more often in CD patients than in the general

population (Green & Jabri, 2006). There is no cure for CD and the only treatment available is compliance with the gluten free (GF) diet. The GF diet consists of elimination of wheat, rye and barley (Green & Cellier, 2007).

### *Gluten Free Diet*

Currently the GF diet is the only therapy and treatment for patients with CD. Non-diet therapies, such as recombinant enzymes that digest the gliadin fractions (a component of gluten), are being investigated (Green & Cellier, 2007); however, their effectiveness has yet to be determined. Instead, it appears that elimination of gluten, which is found in wheat, barley and rye, is critical. The GF diet is the only therapy that is known to alleviate malabsorption and lower the risks of complications, specifically intestinal lymphoma (Ciacci, Iavarone, Mazzacca, & De Rosa, 1998). Non-compliance with the GF diet can lead to both mental and physical ailments, such as lower QoL, refractory sprue and lymphoma (Green & Cellier, 2007).

Non-compliance with the GF diet has been investigated in nation-wide surveys. A national (United States) survey was conducted on 1612 CD patients and found only 68% of the sample to be compliant with the GF diet “all of the time” and 30% to be compliant “most of the time” (Green et al., 2001).

In addition to diet compliance, diet nutrition is being investigated. The GF diet substitutes many grains (wheat, barely, rye) with non-gluten grains and ingredients (rice, tapioca, potato starch). These substitute flours are usually not fortified with B vitamins (Green & Cellier, 2007) and sole reliance on them might lead to vitamin deficiencies. These findings are interesting given the potential role of vitamins B6 (Kado et al., 2005),

B12 (Morris et al., 2005) and folic acid (Feng, Ng, Chuah, Niti, & Kua, 2006; Kado et al., 2005; Mischoulon & Raab, 2007) in cognitive function. Green and Cellier (2007) recommend assessment of vitamins and mineral deficiencies after initiation of the GF diet. These assessments include folic acid, fat soluble vitamins, calcium, iron, and B12.

The research is conflicting about the improvement or alleviation of symptoms associated with CD. For example, Murray et al. (2004) found improvements in diarrhea and weight loss upon introduction of the GF diet. Yet, Midhagen and Hallert (2003) found that 8-12 years on the GF diet did not influence GI symptoms, as the CD patients still had a higher incidence of GI symptoms than the general population. So, it may be the case that GI symptoms improve in CD patients on the GF diet, yet the CD patients will never be equal in symptomology to the general population.

Compliance with the GF diet might increase HRQL in some, since the symptoms have lessened; however, the GF diet may also decrease HRQL in others, due to the social implications and demands of adhering to the diet. Further, there are many conflicting scholarly opinions on how the GF diet impacts HRQL (these will be discussed later).

In addition to the GF diet's impact on HRQL, investigators have also studied its impact on neurological complications. However, in most cases, neurological symptoms have rarely been found to respond to the GF diet.

### *Celiac Disease and Neurology*

#### *Overview*

Neurological symptoms in CD patients have been reported anecdotally, through case studies, and through the use of cross-sectional and retrospective designs.

Neurological symptoms include neuropathy (Kaplan et al., 1988), ataxia (Cooke & Smith, 1966), brain atrophy (Hu et al., 2006), epilepsy (Holmes, 1997), and dementia (Hu et al., 2006). These neurological symptoms occur in about 10% of CD patients (Addolorato et al., 2004; Ghezzi & Zaffaroni, 2001; Holmes, 1997) and can occur in both child and adult onset CD. The prevalence of epilepsy in CD patients has been reported to be between 3.5% - 5.5% (Chapman, Laidlow, Colin-Jones, Eade, & Smith, 1978; Holmes, 1997). Chapman et al. (1978) found that 5% of the CD patients developed epilepsy, while Holmes (1997) found epilepsy in 3.6% of the 388 CD patients that he examined retrospectively. Further, the presence of migraine or tension headaches in CD patients is 46% (Cicarelli et al., 2003). Finally, Cook and Smith (1966) found sensory ataxia in all 16 of their CD patients.

### *Research*

Much of the early research on CD and neurology used anecdotal and single/multiple case study methods to investigate neurological symptoms in CD patients; however, recent research on the neurological complications associated with CD has used both cross-sectional and retrospective designs, to assess the presence of neurological complications in CD patients.

In most cases, neurological symptoms have rarely been found to respond to the GF diet. However, patients with epilepsy and cerebral calcifications have responded slightly to the diet, in that the course of the epilepsy improves with quick initiation of the GF diet upon onset of epileptic seizures, but the disease is not completely cured (Ghezzi

& Zaffaroni, 2001). Further, Collin et al. (1991) found that one patient in their sample of five, with CD, brain atrophy and dementia, responded to the GF diet.

Cooke and Smith's (1966) classic study on malabsorption and CD, which used a case study design, showed that CD patients (11 men; 5 women) did not respond to gluten restriction and upon biopsy showed osteomalacia (5 patients), atrophy and focal loss of neurons (6 patients), purkinje cell loss (5 patients), and spinal cord degeneration (4 patients), spongiform demyelination, and lymphocytic infiltration.

Vaknin et al. (2004) retrospectively evaluated the severity and prevalence of neurological disorders associated with CD. Over the 20 years examined, 148 patients were diagnosed with CD and the neurological abnormalities were listed based on patient charts and then divided into two categories. Twenty-one neurological disorders that could not be attributed to any other condition but CD presented themselves in 12% of the patients ( $n=18$ ). CD diagnosis preceded the neurological abnormalities in 15 of the 18 cases. Neurological disorders that were probably unrelated to CD ( $n=8$ ) were found in 5.5% of the CD sample. The exact mechanism for these disturbances is not known; however, malabsorption of nutrients, absorption of toxic substances, deficiency states, metabolic abnormalities, or immune-mediated mechanisms are potential mechanisms (Vaknin et al., 2004).

Zelnik, Pacht, Obeid, and Lerner (2004) conducted a study to investigate the association between more common or "soft" neurological concerns and CD in adolescents and children ( $n=111$ ) and an age- and gender-matched control group ( $n=211$ ). CD patients were more likely to develop neurological disorders, hypotonia,

developmental delay, learning disorders, attention deficit hyperactivity disorder (ADHD), headache, and cerebellar ataxia, when compared to the control subjects (51.4% vs. 19.9%) (Zelnik et al., 2004). The GF diet only benefited those with infantile hypotonia and migraines or non-specific headache.

Kieslich et al. (2001) found neurological abnormalities in 10 of 75 pediatric CD patients and white-matter lesions in 20% of the 75 pediatric CD patients. All patients were on the GF diet for approximately 2.4 years and the white-matter lesions were not related to GF diet compliance or GI symptoms (Kieslich et al., 2001).

Addolorato et al. (2001) investigated brain perfusion changes, using cerebral single photon emission computed tomography examination, in 15 CD patients not on the GF diet, 15 CD patients on the GF diet for 1-year, and 24 healthy controls. The CD patients not on the GF diet had significantly lower cerebral perfusion in the frontal and parietal lobes than the healthy controls (11 of the 15 CD non-GF diet patients had one hypoperfused brain area vs. 0 of the 25 controls). There were no differences between the CD GF diet patients and the controls (1 of the 15 GF diet patients had one hypoperfused brain area vs. 0 of the 25 controls).

Carta et al. (2002) investigated the role of thyroid disorders, anxiety disorders, and depressive disorders in 36 CD patients and 144 healthy sex- and age-matched controls since thyroid disease is present in CD patients and hypothyroidism may be an additional risk factor for psychiatric disorders. Using psychiatric evaluations, guided by the DSM-IV criteria and thyroid evaluations, they found that CD patients had higher lifetime and 6-month major depressive disorder and panic disorder than the control

group. Symptoms of CD were reported at an earlier age (12.8 years vs. 21.5 years) in CD patients with major depressive disorder than CD patients without major depressive disorder. When thyroid disease was assessed, Carta et al. found a higher prevalence of anti-thyroid autoantibodies in CD patients than in the control group (30.5% vs. 9.7%). Most interesting was the association between panic disorder, major depressive disorder, and anti-thyroid antibodies, in that there was a higher frequency of panic disorder and major depressive disorder found in CD patients with positive anti-thyroid autoantibodies. The association between CD, hypothyroidism, and depression provides support for thyroid disease being a potential mechanism of depression in CD patients. Possible explanations for this mechanism include the effect of the symptoms of both hypothyroidism and CD on energy levels (fatigue) and therefore, one's ability to sustain activity and a high level of QoL.

#### *Proposed Mechanisms*

In addition to the thyroid mechanisms mentioned above and the potential mechanisms listed by Vaknin et al. (2004), there are some other hypotheses that have been used to explain the presence of neurological manifestations in CD patients.

First, nutritional issues, such as vitamin malabsorption, B-12 deficiency, and folic acid deficiency, may be involved in central nervous system (CNS) functioning. The data supporting these hypotheses are mixed and inconclusive; however in some studies, folate has been found to be associated with depression (Bjelland, Ueland, & Vollset, 2003; Bottiglieri, 2005; Carney, 1967; Tiemeier et al., 2002) and neurodegenerative disorders (Hu et al., 2006). Also, Kupper (2005) reviewed studies that addressed CD and the GF

diet and found that lesion pronouncement in the small intestine was negatively related to vitamin (folate, B12) and mineral (iron, copper) levels. Also, correlations have been found between zinc deficiency and the severity of the villi atrophy (Kupper, 2005).

Second, the presence of antigliadin antibodies, as noted in Hadjivassiliou et al. (1996), may be associated with neurological deficiencies in CD patients. Antigliadin antibodies, which can be measured by a serologic test, are positive in the presence of gluten. Therefore, inflammation, tissue damage, and villous atrophy have probably occurred. The presence of these symptoms, and thus expansion of the B cells to produce antibodies could be linked to neurological deficiencies, especially those due to malabsorption of vitamins and minerals.

Third, the metabolism of biogenic amines in the CNS may play a role in mental illness in CD patients. The monoamine hypothesis is the most supported hypothesis in the CD literature. Monoamines include catecholamines and serotonin which are synthesized from tyrosine and tryptophan, respectively. This hypothesis has been tested by examining the ratio of tyrosine to the sum of large neutral amino acids and the ratio of tryptophan to the sum of the remaining large amino acids. A lower plasma tyrosine or tryptophan ratio could be indicative of lower availability of these amino acids to the brain. Hernanz and Palaneo (1991) conducted this analysis in 27 CD children, with 15 of them not on the GF diet, and 12 of them on the GF diet, and 12 control subjects. Compared to the control group, CD children, adhering and not adhering to the GF diet had significantly lower plasma tryptophan ratios. Also, the non-GF diet CD children had significantly lower plasma tryptophan ratios than the GF diet CD children. The authors

suggested that the lowered tryptophan ratio may be suggestive of decreased serotonin levels (Hernanz & Polanco, 1991). Reduced availability of serotonin to the brain may be related to depression, mood, and behavioral disturbances.

Fourth, CD patients who are not on the GF diet have been found to have low levels of Crithidia fasciculata, a growth factor for bipterin compounds. A reduction in these bipterin compounds, which act as co-factors for the synthesis of dopamine, norepinephrine, epinephrine, tyrosine, and tryptophan, may result in low levels of these important amino acids and neurotransmitters (Cooke, 1978).

### *Celiac Disease and Cognitive Performance*

#### *Overview and Research*

Although there have been numerous studies conducted on the physiology of these neurological complications, research investigating cognitive performance and behavioral implications as a result of these neurological deficiencies has been rare. In fact, only three articles have been identified that employed cognitive performance tests. One study was designed to solely assess cognitive behaviors (Hallert & Astrom, 1983) while another research study incorporated neuropsychological tests as a means, among others, to describe sporadic cerebellar ataxia with gluten sensitivity (Burk et al., 2001).

Hallert and Astrom (1983) assessed the intellectual ability of 19 untreated Swedish CD adults, with a mean age of 48 years. The test battery, consisted of The Synonyms Reasoning Block (SRB) test (includes Koh's Block design test), Thurston's memory test, reaction time with simple stimulation and 3-choice stimulation, figure identification, finger dexterity, figure rotation, design, street, organic integrity test (OIT)

and Benton's visual retention test. The results showed no cognitive impairment in adult CD based on scores of the CD patients on the neurological tests compared to scores of general population samples. Interpretation of these results is difficult for a couple of reasons. Although the CD patients were not behaviorally impaired, it is important to remember that neurological complications could still be present, since it has been reported that approximately 10% of CD patients experience neurological complications (Addolorato et al., 2001; Ghezzi & Zaffaroni, 2001; Holmes, 1997). In addition, the cognitive tests that were used did not focus on measures of executive functioning, thus the test battery was not inclusive of all potentially impacted measures of cognition. Lastly, even though the tests are supposed to be sensitive to cognitive impairments, only subtle impairments were present. Therefore, the combination of small sample size, a failure to include primary measures of executive function, and small cognitive deficits could have resulted in nonsignificant findings.

Burk et al. (2001) investigated sporadic cerebellar ataxia that was associated with gluten sensitivity (screened for antigliadin and antiendomysium antibodies) in 104 patients with ataxia. Twelve of the 104 had gluten sensitivity. Neuropsychological features were also described in eight of the 12 patients that had positive antibodies and nine control subjects after a series of tests were administered. The tests included the Mini Mental State Exam, Verbal IQ, Performance IQ, Digit Span Forward, Digit Span Backward, Wechsler Memory Scale (immediate and delayed recall), Word Lists (immediate and delayed recall of consecutive, randomized, and uncategorized lists), Rey-Osterrieth complex figure, Verbal fluency, and the Wisconsin Card Sorting Task.

Cognitive tests that are applicable to the current study's design and/or those which showed significant differences between the ataxia patients with gluten sensitivity and the controls are presented in Table 1.

Table 1  
*Means and Standard Deviations for Relevant and Significant Neuropsychological Tests*

Cognitive tests <sup>a</sup>	Control (N=9) M (SD)	Patient (N=8) M (SD)
MMSE	29.6 (0.7)	29.4 (1.1)
Digit Span (backwards)	5.1 (1.5)	5.0 (1.2)
Wisconsin Card Sorting Test – Categories	5.9 (0.3)	3.7 (2.4)*
Verbal Fluency – phonemic category	12.2 (2.9)	8.5 (2.1)**
Verbal Fluency – alternating semantic category	15.2 (2.8)	12.4 (2.3)*
Word Lists – consecutive categories list	9.8 (2.8)	5.9 (1.5)***,+
Word Lists – uncategorized list	7.0 (1.6)	3.5 (2.0)***,+
Wechsler Memory Scale – immediate recall	12.8 (2.6)	7.8 (2.5)***,+
Wechsler Memory Scale – delayed recall	10.3 (2.6)	6.5 (2.5)**

*Note.* \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.005$  compared to controls; +Bonferroni-Holm adjusted  $p$  values; <sup>a</sup> = higher score is better performance on all tests; Table data from Burk et al. (2001)

Finally, Hu et al. (2006), retrospectively examined the Mayo Clinic data, between 1970 and 2005, and reported cognitive test results for five of their 13 CD patients. Thirteen biopsy diagnosed CD patients (5 women; 8 men) who experienced progressive cognitive decline within two years of their CD diagnosis were examined. The mean age of cognitive impairment was 64 years. The most common cognitive complaint was amnesia ( $n=12$ ) and the most common symptom was gait ataxia ( $n = 10$ ). The Short Test of Mental Status was obtained for nine patients and the average score was a 28 (total 38; range 18-34). Five of the 13 patients had neuropsychological test results. Scores from the learning, memory, processing speed, and intellectual intelligence tests indicated that

two patients had global cognitive impairment, one patient had memory deficits, and two patients had learning inefficiency (Hu et al., 2006). An EEG was obtained for nine of the 13 CD patients and eight of the nine CD patients showed different patterns of EEG activity than were observed in healthy normal EEGs. MRIs were performed on seven CD patients and six CD patients had generalized atrophy and one had frontal atrophy. Five CD patients had computerized tomography of the head and generalized atrophy was found in four and dense basal ganglia calcifications were found in one. Nutritional deficiencies were assessed in six patients, with two having B12 deficiencies and three having folate deficiency. Upon supplementation, cognition was not improved. At follow-up, 10 patients had cognitive deterioration, with nine of the 10 dying from progressive dementia (Hu et al., 2006). The GF diet was only effective in helping three of the 13 CD patients, who had stabilization, but not improvements, in their cognitive function.

#### *Future Directions in Celiac Disease, Neurology and Cognitive Research*

According to the literature that has assessed the neurology of CD patients, brain atrophy, deterioration of the cerebellum, brainstem nuclei, spinal cord, and deep gray masses (Kinney et al., 1982) have been found, along with lesions within the white matter of the brainstem, cerebellum, and cerebrum (Ghezzi et al., 1997). Focal, diffused, or nonspecific frontal lobe changes, generalized atrophy, and dense basal ganglia calcifications have been also found in CD patients (Hu et al., 2006). Further, lower cerebral perfusion in the frontal and parietal lobes were found in CD patients (Addolorato et al., 2004).

Knowing that these brain areas are affected, specifically the frontal and parietal lobes, encourages future research to use cognitive testing to assess executive functions specifically associated with those regions. Executive functions are hampered when frontal lobe damage occurs or there is injury to the prefrontal regions. White matter lesions have been associated with reduced processing speed, memory and executive functions (Gunning-Dixon & Raz, 2003). Further, fluid intelligence, an executive function, was found to be associated with white matter lesions (Leaper et al., 2001). Multiple Sclerosis patients with brain atrophy showed lower scores on executive function tests, PASAT, Digit Span Backwards, and short-term memory (Morgen et al., 2005). Further, low cognitive performance on the Stroop and word fluency was found in men with frontal cortical atrophy (Soderlund, Nyberg, & Nilsson, 2004). Although there has been research on executive function in other populations, the CD population has rarely been studied. Due to the lack of research in this area with CD patients, more investigations must be conducted to see if the neurological complications that have been described in the literature are affecting cognitive behaviors. This gap in the literature has led me to propose assessing cognitive function in CD patients, specifically executive functions that have been shown to be linked to frontal and parietal lobe changes.

## *Celiac Disease and Health-Related Quality of Life*

### *Overview*

QoL and HRQL have been measured in healthy adults, older adults, and chronic disease patients. These terms are sometimes used interchangeably, with the term, “quality of life” being replaced by HRQL or health status in many of the medical research studies. Well-being has also been used, specifically by the World Health Organization (WHO), as a component in the definition of health. The WHO defines health as “a state of complete physical, mental, and social well-being and not merely an absence of disease or infirmity”(World Health Organization, 1946). Both the psychology literature and exercise literature have defined QoL. In the psychology literature, QoL has been defined by Pavot and Diener (1993) as satisfaction with life that is determined by a “conscious cognitive judgment”, while in the exercise literature, QoL has been defined as evaluations, both subjective and objective, of both the “goodness” of one’s overall life and the domains that are present in one’s life (Lox, Martin Ginis, & Petruzzello, 2006). HRQL focuses specifically on QoL areas that can be affected by health interventions. Examples include physical function, emotional well-being, and social roles (Lox et al., 2006). Finally, HRQL is more than just an objective measure of health – it is the individuals’ perception of his/her health and how health or specific health variables impact functioning and overall life.

HRQL is an important consideration for CD patients due to their need for lifelong adherence to the GF diet and the complications of having a chronic disease. HRQL is becoming recognized as an important primary or secondary assessment in

gastroenterology studies. The NIH now mandates that any study that assesses GI disease must also assess HRQL.

Most research on HRQL and CD has been designed to assess whether or not adherence to the GF diet is associated with differences in important HRQL outcomes. Similar to the impact of the GF diet on depression, the research has investigated the impact of the GF diet on HRQL and has found mixed results. In these research studies, HRQL has been assessed either with a survey created by the investigators and/or the SF-36. Recently, the Celiac Disease Questionnaire (CDQ) (Hauser, Gold, Stallmach, Caspary, & Stein, 2007) was created and validated and is now being used solely or in conjunction with the SF-36 in research dated post-2006. In reviewing the extant literature, both QoL and HRQL have been examined in CD using a variety of measures.

#### *Research*

Most research has found that HRQL is impaired in CD patients; however, others (Viljamaa et al., 2005) have found no differences between the CD patients and controls on HRQL or anxiety/depression measures (Roos, Karner, & Hallert, 2006). For example, Viljamaa et al. investigated screen-detected CD patients who had adhered (94.5% adherence rate) to the GF diet for 14 years. Fifty-three screen detected CD patients were compared to one of three control groups (symptom detected CD patients, untreated CD patients (not on GF diet) and non-Celiac patients). Screen-detected CD patients were obtained and diagnosed with CD by screening at-risk groups, while symptom-detected CD patients were diagnosed after complaining of GI issues. HRQL was assessed with the SF-36 and no difference was found in levels of HRQL between the screen-detected

CD patients and the two control groups (symptom-detected CD patients, and non-Celiac). Those CD patients who did not adhere to the GF diet had lower HRQL and more GI symptoms than the CD patients in the other groups.

Ciacci et al. (2003) used a cross-sectional design to evaluate self-perceived QoL in 581 CD patients (410 women). Ciacci et al. (2003) contacted 745 CD patients who were currently on a GF diet. Of those contacted, 581 agreed to participate (78% response rate; average of 8.26 years on the GF diet). The questionnaire assessed the CD patients' level of knowledge about the disease, diet compliance, depression, anxiety, and positive attitudes. Diet adherence was high, in that 74.1% of the CD patients had full GF diet compliance. Feelings of overall well-being were assessed on a 4-point scale, with very well, well, "so,so", and bad being the available selections. Forty-seven percent of the CD patients reported that they felt "very well". Most interesting were the somewhat contradictory differences reported for depression/anxiety and happiness. That is, 56.6% and 74.3% of the CD patients reported that they "rarely" feel anxious or depressed, yet 45.6% of the CD patients reported that they were not happy (Ciacci et al., 2003). Difficulties in social interactions may explain some of the unhappiness (Ciacci et al., 2003), since 25.6% of CD patients expressed "feeling uneasy at the eating table on "several occasions", while 10.4% and 6.2% of CD patients reported feeling uneasy and feeling different "often". Two weakness of this study include the lack of a healthy control group and the reluctance to explain the variability in responses to the depression/anxiety and happiness questions. One would think that a lack of depression or anxiety equates to happiness, but this study did not show that. Further, it may be that

other QoL variables, other than the variables examined in this study, could shed light on what determines “happiness” in CD patients. It also may be that a general depression, anxiety, and happiness scale might not truly measure these variables, and that specific questions pertaining to CD must be asked.

Casellas, Lopez Vivancos, and Malagelda (2005) investigated the effect of the GF diet by assessing 63 CD patients and identifying them as being in one of two groups based on their current compliance with the GF diet. Fifty-four CD patients were in the GF diet treatment group since prior to the study they were on the GF diet, while 9 CD patients were considered to be in the no-treatment group since they had not begun the GF diet as of yet. Compliance to the GF diet was assessed with a modified version of the questionnaire used by Morisky, Green, and Levine (1986), while the Spanish version of the Euro5D (EuroQoL-5D) and Gastrointestinal Quality of Life were used to assess HRQL. Compliance to the diet in the GF diet treatment group was 79%. There was a statistically significant difference between the GF diet treatment group and the no-treatment group with the treatment group having better HRQL than the no-treatment group. Further, those in the treatment group who reported “symptoms disappeared with the diet” reported better overall HRQL than those in the treatment group who reported “partial improvements only”. Finally, the results from the EuroQoL-5D in this study were compared to a healthy Spanish sample. Median scores for the treatment group were similar to the median scores obtained in the healthy Spanish population and median scores for the no-treatment group were lower than the median scores in the healthy Spanish population.

Hauser et al. (2006) conducted a national survey to assess HRQL in German CD patients as compared to the German population. Questionnaires assessing HRQL (SF-36), depression (Hospital Anxiety and Depression Scale; HADS), and bodily symptoms (fatigue, dyspeptic myalgia/arthritis and cardiorespiratory) (GieBener Symptom Check List; GBB 24) were mailed to 1000 of the 18,355 members of the German Coeliac Society DZG. Fifty two percent of the surveys were returned, with 71.7% of the sample being female. The median age was 44.4 years and 45% of the sample reported having one or more diseases associated with CD. The results indicated that 26% of the sample had symptoms of irritable bowel syndrome. CD patients had higher anxiety scores and lower HRQL scores (except for physical functioning) than the general population; however, there was no difference between groups for the depression measure. Pre-CD diagnosis, 71% rated global HRQL as “bad”; however, after diagnosis of CD and initiation of the GF diet, 98% reported a reduction in symptoms and 73% reported “very much better” or “much better” global HRQL. The GF diet was able to help improve HRQL in GD patients, yet, HRQL was still significantly lower in CD patients on the GF diet when compared to the general German population.

Like Hauser et al. (2006), Hallert et al. (1998) found that CD patients on a GF diet for 10 years had lower QoL than the general population. Hauser et al. and Hallert et al. found that adherence to the GF diet is related to QoL, but that the GF diet alone does not make CD patients similar to the general population in terms of QoL. Other research has not shown this. For example, Roos, Karner, and Hallert (2006) found no difference in anxiety, depressed mood, or distress, as measured by the Psychological General Well

Being Index (PGWB), between Swedish CD adults ( $n=51$ ) and population controls ( $n=182$ ) after the CD adults had been treated with the GF diet for 8-12 years. However, the Swedish CD women in this study had a lower level of PGWB than the Swedish CD men.

Using the same sample, Hauser et al. (2007) further investigated HRQL, by determining predictors of HRQL through a multivariate approach. Five hundred and twenty-two CD individuals (78% female) participated and 41% of these were biopsy-diagnosed. Hauser et al. found that the adherence to the GF diet and not the duration of the GF diet were predictive of scores on the Celiac Disease Questionnaire (CDQ). That is, those who were non-compliant with the diet were more likely to have lower scores on the CDQ, which measured GI symptoms, emotional well-being, social restrictions, and disease-related worries.

*Social and environmental factors affecting HRQL and QoL.* The definition of HRQL includes how content and happy individuals are with many facets of their life. These facets include social functioning, physical functioning and mental functioning. In addition to mental functioning, social functioning is an important area of concern for individuals with CD. Environmental factors influence perception of QoL and Ciacci (2006) mentions how sources of GF foods and the availability of GF foods in specific countries may impact the burden placed on CD patients. Further, social and environmental factors such as the patient's education and quality of healthcare may influence how a CD patient adapts to the GF diet. One study showed how women had a higher perceived "burden of illness" when compared to men. This might be due to the

social implications of the disease, such as shopping for food, cooking, and feeding their family. This feeling of restriction in selecting foods may impact their QoL. In addition to social and environmental factors, feelings of an unsatisfactory sex life (Ciacci et al., 2003) and difficulty adapting to a chronic disease (Fera, Cascio, Angelini, Martini, & Guidetti, 2003) have been reported.

Lee and Newman (2003) investigated the impact of the GF diet on QoL in 253 CD patients (74% female). Through mail, Lee and Newman (2003) received back 68% of their surveys, which were self-administered questionnaires that assessed demographics, lifestyle, and food choices, and asked 11 questions from the SF-36 to assess perceived health, impact of disease, and socialization. The results of this study are interesting in that although CD patients reported that CD had no effect on their ability to work (81% of respondents) and that their current health was perceived as “excellent” (71% of respondents), 82% of CD patients reported a negative impact on other “specific” QoL issues (travel, family life, dining out, and careers). Further, there were gender differences noted, as more women than men were impacted in all areas. These results support the need to continue to assess specific CD-related QoL issues, in that general QoL variables, such as overall ability to work or overall health might not be the best predictors of QoL in CD patients.

*Doctor-patient and nutritionist-patient communication.* Access to information concerning how to adhere to the GF diet and knowledge about the disease also affects QoL and HRQL. For example, Hauser et al. (2007) found that doctor-patient communication was a predictor of HRQL via the CDQ scores. Further, there was a

significant correlation between the total CDQ score and both non-compliance with the GF diet and dissatisfaction with information received from the doctor. That is, total CDQ was reduced in those who had high non-compliance and high dissatisfaction with information provided by their doctors (Häuser et al., 2007). Adherence to the GF diet has been shown to cause lower levels of QoL, with one possible cause being the lack of information available to CD patients from the medical community. Tidwell and Bomba (2001) showed that of the 96 CD patients who saw a dietician, 53.3% of CD patients rated sessions with a dietician as unhelpful and also found that 54.1% found the dietician to not even know about CD. Therefore, based on this research there may be a link between interactions with the medical community, knowledge about the disease and GF diet, diet adherence, and HRQL. Just as plausible, is that anxiety and depression impact diet adherence, in that high levels of anxiety and depression are associated with reduced GF diet adherence (Addolorato, Stefanini, & Capista, 1996). For example, depression has been found to be one of the main reasons for noncompliance to treatment in chronic disease patients (DiMatteo, Lepper, & Croghan, 2000).

*Personality, quality of life and celiac disease.* Some research has tried to link personality factors to QoL in CD patients. For example, De Rosa, Troncone, Vacca, and Ciacci (2004) investigated how the chronic nature of CD and the GF diet requirements impacted personality and diet adherence. Twenty-nine CD patients (25 women) and 47 control subjects were assessed with the Italian version of the Eysenck Personality Questionnaire and the Psychophysiological Questionnaire. CD patients were following a GF diet and rated their adherence to the GF diet on a scale of 0 to 10, with 10 being that

they always adhered. The CD patients, but not the controls, completed the Italian version of the Illness Behavior Questionnaire. Results showed an average adherence rate to the GF diet of 8.63. Duration of having the disease was an important predictor of emotional instability, as measured by the Eysenck Personality Questionnaire. That is, CD patients who were diagnosed as children had lower emotional instability scores than those diagnosed later in life. Further, CD patients were found to have higher scores on the irritability scale and affective inhibition scale, and higher anxious vigilance and a higher tendency to conform than the control subjects (De Rosa et al., 2004).

*Other complications associated with celiac disease and their impact on HRQL.*

Other complications, although not neurological in nature, affect CD patients and may contribute to their lower levels of HRQL, especially since they affect their mobility and energy or lack thereof. Osteoporosis and iron deficiency anemia are present in some CD patients. For example, Green and Jabri (2006) reported a prevalence of CD in 2-7% of the osteoporosis patients and 3-15% of the iron-deficiency anemia patients that were screened. Hauser et al. (2007) found that 15% of their CD sample ( $n=522$ ) had osteoporosis, while 10% of the sample had anemia. Although iron deficiency anemia is usually corrected with the GF diet (Kupper, 2005), osteopenia and osteoporosis are increased in CD patients not on the GF diet, and are only sometimes stabilized in CD patients on a GF diet.

*Future Directions in Celiac Disease and HRQL Research*

Currently, all of the CD and HRQL research has focused on the impact of the GF diet on HRQL variables. The results have been mixed in that some research has found

that CD patients currently adhering to the GF diet were not different from the healthy controls (Viljamaa et al., 2005); however, other research has found that the GF diet is at times able to improve HRQL, but not normalize it (Häuser et al., 2006). Therefore, knowing that the GF diet may not be able to normalize HRQL in CD patients, other variables that have been shown to impact HRQL should be investigated in the CD populations. Specifically, the influence of physical activity and aerobic fitness on CD patients should be explored.

### *Physical Activity and Aerobic Fitness*

#### *Defining the Terms*

Physical activity is defined as “any bodily movement produced by the contraction of skeletal muscle and that substantially increases energy expenditure” American College of Sports Medicine (2006, p.3) and is usually measured in kilocalories per unit of time (Casperson, Powell, & Christenson, 1985). According to Buckworth and Dishman (2002, p.29) “aerobic fitness refers to the maximal capacity of the cardiovascular system to take up and use oxygen and is typically expressed in millimeters of oxygen per minute adjusted for total body mass or fat free mass expressed in kilograms”. Based upon the link between physical activity (the behavior) and aerobic fitness (a reflection of genetic factors, physiological status, and level of physical activity), it is predicted that both may influence psychological outcomes in CD patients.

### *Physical Mobility and Functional Fitness*

Physical mobility, or one's independent ability to perform activities of daily living (ADL), is measured through neuromuscular examination, self-report questionnaires, clinical laboratory balance or sway tests, and field tests that assess movements used in daily living (Podsiadlo & Richardson, 1991). Although physical ability is not our primary aim, the need to be able to function effectively is an important consideration when assessing other variables, such as physical activity levels, HRQL, and executive function, which are both closely related to physical functioning. Stewart, King and Haskell (1993) proposed that functioning and well-being were the two broad qualities used to label outcomes for quality of life research. The functioning category included physical abilities and ADLs. Rejeski, Brawley, and Shumaker (1996) found that correlation were higher between performance-based measures of dysfunction and HRQL than for fitness and HRQL; therefore, measuring physical mobility might provide us with additional information as to what measures of physical activity or aerobic fitness are important as predictors. Further, the Timed Up and Go task, our measure of functional fitness requires cognitive demands, specifically executive processes. For example, a participant is asked to stand from a chair quickly, walk as fast as possible to a cone, turn around as quickly as they can, walk as fast as possible back to the chair, and sit down. This process requires planning (how will I get to the cone and back), formulating a goal (when she says, "Go", I am going to stand as quickly as I can...), initiating that goal, self-monitoring their behavior (did I go quickly enough?), and correcting their behavior (let

me try to go faster this time), if needed. These abilities and processes are all part of executive functions (Salthouse, Atkinson, & Berish, 2003)

### *Physical Activity, Aerobic Fitness and HRQL*

#### *Overview*

In the CD population, the effect of physical activity and aerobic fitness on HRQL has not been studied. However, there has been one pilot correlational study (see Chapter III) that has investigated the relationship between HRQL and satisfaction with life (SWL) with physical activity (Barella, Etnier, Gill, & Perry, 2008). Further, numerous studies have reported the impact of physical activity on HRQL in other populations including older adults (Elavsky et al., 2005; Rejeski & Mihalko, 2001; Schechtman & Ory, 2001), cancer patients (Courneya & Friedenreich, 1999), fibromyalgia patients (Mannerkorpi, Nyberg, Ahlmen, & Ekdahl, 2000), chronic obstructive pulmonary disease patients (Katula, Rejeski, Wickley, & Berry, 2004; Lacasse et al., 1996), cardiac rehabilitation patients (Denollet & Brutsaert, 1995), knee osteoarthritis patients (Rejeski, Ettinger, Martin, & Morgan, 1998; Rejeski, Martin, Miller, Ettinger, & Rapp, 1998); people with cardiac disease risk factors (Taylor-Piliae, Haskell, Waters, & Froelicher, 2006), intensive care patients (Patrick, Danis, Southerland, & Hong, 1998), and multiple sclerosis (Sutherland, Andersen, & Stoové, 2001).

#### *Research*

Since the effect of physical activity has not been addressed in CD patients, except in the case of the pilot correlational study, literature from other populations, including many of the above-mentioned groups, will be assessed, first by addressing literature

reviews on the area of physical activity and QoL or HRQL and then by assessing cross sectional studies and interventions. The pilot study that assessed the relationship between physical activity, aerobic fitness, HRQL, and satisfaction with life (SWL) will also be discussed in detail.

First, a literature review was conducted to assess the effect of physical exercise on a broad range of QoL and HRQL variables following a cancer diagnosis (Courneya & Friedenreich, 1999). Twenty-four studies were reviewed, eighteen of which were interventions. The results from 16 of the 18 intervention studies and five of the six descriptive studies reported a positive effect for physical exercise following a cancer diagnosis on physical, functional, psychological, and emotional well-being (Courneya & Friedenreich, 1999).

In their review of 28 studies, Rejeski, Brawley, and Shumanker (1996) concluded that there was direct evidence for a relationship between physical activity and HRQL. Of the 28 studies, 18 examined chronic disease populations (cardiovascular disease, pulmonary disease, and arthritis), while the other 10 examined asymptomatic adults. Age, activity status, or health of participants did not matter for improvements in HRQL to occur. Rejeski et al. (1996) reported from their review that changes in fitness ( $VO_2$ ) did not impact HRQL as much as performance based measures of dysfunction. That is, in the populations studied, maximal oxygen carrying capacity was not the best indicator of changes in HRQL.

Social support, a domain of HRQL, may be important for health in chronic disease populations, especially if it can alter the impact of the illness on the patient

(Sherbourne, Meredith, Rogers, & Ware, 1992). In the CD population, this variable is extremely important given the social implications of the CD diet. Sherbourne et al. (1992) examined, using a cross sectional design, how social support and stressful life events impact physical functioning and emotional well-being in four chronic disease groups (diabetes, coronary heart disease, hypertension, depression) of varying ages. The Medical Outcomes Study (MOS) participants provided data for this study. Eligible patients ( $n=1402$ ) completed surveys that assessed HRQL, social support, and stressful life events. The analyses were conducted in age groups (18-44; 45-64; and 65 years +). The 1402 participants from the MOS group were compared to 2181 patients of other medical offices. Social support was beneficial to QoL in all age groups, with the high social support group having greater physical functioning and emotional well-being than the low social support group. Stressful life events also impact HRQL, with the impact being on emotional well-being more than on physical functioning, but varying according to age group. For example, only the 45-64 year olds with financial concerns experienced a lower physical functioning and emotional wellbeing at baseline and over time than those 45-64 year olds without financial concerns. Finally, relationship events (serious arguments, divorce or termination of a relationship) only impacted emotional well-being and all age-groups who experienced relationship events had lower emotional well-being at baseline than those who did not experience relationship events.

In addition to the chronic disease conditions investigated by Sherbourne et al. (1992), HRQL has been found to be hampered in Fibromyalgia Syndrome (FMS)

patients, chronic obstructive pulmonary disease patients, and patients with multiple sclerosis (MS).

FMS symptomatically appears in patients as fatigue, pain, stiffness, and functional limitations. Fatigue is also a symptom experienced by CD patients; therefore, Mannerkorpi et al. (2000) reported on the effects of a physical activity intervention in FMS patients. Fifty-eight women (mean age = 46 years) with FMS participated in either 6-months of 35-minute pool sessions and six 1-hour education sessions or the control condition. Mannerkorpi et al. used both self-report questionnaires (Fibromyalgia Impact Questionnaire (FIQ), SF-36, Swedish version of the Multidimensional Pain Inventory, The Arthritis Self-Efficacy Scales, The Arthritis Impact Measurement Scales, and The Quality of Life Questionnaire) and physical activity assessments (6-minute walk test, chair test, shoulder range of motion, grip strength, shoulder abductor endurance) at pre-intervention and at the end of the study. The chair test was used to assess lower body endurance and required the participant to stand up and sit down as fast and as many times as possible in one minute (Mannerkorpi et al., 2000; Mannerkorpi, Svantesson, Carlsson, & Ekdahl, 1999).

Significant differences were found for the 6-minute walk test between the exercise and control groups. Further, the exercise group performed better on the FIQ total and FIQ physical functioning scores. Finally, when comparing the exercise to control groups, the exercise group had significant improvements in SF-36 general health, SF-36 social functioning, anxiety, and affective distress. When with-in effects were assessed, the exercise training group had improvements from pre- to post-6-month

intervention in physical functioning, bodily pain, general health, vitality, and social functioning domains on the SF-36. Fatigue and anxiety also improved. Since the aerobic training program was combined with an education component, it is impossible to determine the specific influence of the aerobic training component on the changes observed.

Other medical conditions, such as, chronic obstructive pulmonary disease (COPD), have benefited from exercise training (Lacasse et al., 1996). Lacasse et al. (1996) conducted a meta-analytic review of COPD patients involved in randomized controlled trials that involved at least 4-weeks of exercise training and assessed either functional or maximal exercise capacity and/or HRQL. The randomized controlled-trials were classified according to the exercise setting, component of the intervention, duration of the intervention, exercise capacity outcome, and HRQL outcome. Fourteen trials were included in this analysis. Twelve of the 14 trials assessed HRQL, 11 of the 14 trials ( $n=309$  patients) measured maximal aerobic capacity and 11 of the 14 trials ( $n=413$  patients) measured functional exercise capacity. The HRQL analyses were limited to studies that included two instruments, the transitional dyspnea index and the chronic respiratory index. Lacasse et al. (1996) justified this limitation by noting that only these two instruments have published validity and reliability; however, that assessment might not be accurate since the Profile of Moods (POMS) and others have published validity and reliability. The effect of respiratory rehabilitation on dyspnea ( $ES=0.8$ ), fatigue ( $ES=0.6$ ), emotional function ( $ES=0.5$ ), and mastery ( $ES=0.6$ ) were found. All of these effects for the QoL outcomes exceeded the minimally clinically important difference;

therefore, providing clinical evidence supporting of the benefits of the rehabilitation program.

Although patients with multiple sclerosis (MS) are often told not to exercise, participating in aerobic exercise may help lessen fatigue symptoms, which have been found in MS patients (Sutherland et al., 2001). Sutherland et al. (2001) investigated if 10-weeks of aerobic exercise were able to affect psychological well-being and HRQL. Twenty-two MS patients were randomly assigned to either the exercise condition, which consisted of a submaximal exercise test on a cycle ergometer pre- and post-intervention, followed by 10-weeks of supervised water-based training sessions (3X/week for 45 minutes each session), or the control condition. HRQL was measured using The Multiple Sclerosis Quality of Life-54 (Vickrey, Hays, Harooni, Myers, & Ellison, 1995), which contains all questions from the SF-36 and items specific to MS patients. Mood was measured with the Profile of Mood States – Short Form (POMS-SF) (Shacham, 1983), while social support was measured with the Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet, Dahlem, Zimet, & Farley, 1988). When the exercise group was compared to the control group, the largest effects were found for energy ( $\eta^2 = .51$ ) and vigor ( $\eta^2 = .55$ ).

In addition to chronic disease populations, physical activity has been shown to increase QoL in older adults (Elavsky et al., 2005; Rejeski & Mihalko, 2001). For example, Ettinger et al. (1997) investigated QoL (self-reported disability score, knee pain score, performance measures of physical function, x-ray score, aerobic capacity, and knee muscle strength) in 439 older adults, with knee osteoarthritis, who were part of The

Fitness Arthritis and Seniors Trial (FAST). Participants were randomized to one of three groups, aerobic training, resistance training, or a health education control group. The results of this randomized clinical trial showed that older adults with knee disability who participated in either the aerobic conditioning or resistance training condition reported lower physical disability, lower knee pain, better 6-minute walk test, better time to climb and descend stairs, better time to lift and carry 10 lbs, and better time to get in and out of the car than the health education group.

Gill, Williams, Williams, Butki, and Kim (1997) investigated the relationship between physical activity and psychological well-being in 130 healthy older women (mean age = 74.8 years) using demographic, activity efficacy, health and well-being, general well-being, and activity measures. More than half of the sample ( $n=63$ ) had fallen. Forty-five participants participated in organized exercise 2-3 times per week, while 96 participants walked about 4.4 times per week. The results showed that overall, higher total activity predicted greater psychological well-being, age was not related to well-being, and activity was correlated stronger with the health and well-being ratings and activity efficacy than general well-being.

In addition to chronic disease populations, and older adults, QoL has also been investigated in younger, healthy adults. Specifically, King, Taylor, Haskell, and DeBusk (1989) tested 120 sedentary healthy middle-aged adults who were randomized to either the treatment or control condition. If randomized to the treatment condition, participants completed a 6-month home-based aerobic exercise program which consisted of approximately 47-54 minutes at 65% to 77% of peak baseline treadmill heart rate. At

baseline and 6-months, body weight and oxygen uptake were measured. Psychological measures were assessed at baseline and biweekly, for a total of 13 scores. A 14-item rating scale developed for this research study was used. When compared to the controls, the exercise condition showed significant improvements in the mean rates of change and actual mean ratings across time in satisfaction with current shape and appearance, current physical fitness level, and satisfaction with current weight (King et al., 1989). Even when expectations for change were used as a covariate in the analysis, these three remained significant. Most interesting was that the change in  $VO_2$  max was not correlated with any of the other measures, except body weight. Therefore, aerobic fitness may not be the mechanism that is causing these changes in psychological health. Other factors, such as perceived body image and social support during exercise could be important in predicting psychological health.

Finally, HRQL and SWL were assessed in CD patients during a pilot/preliminary study. The preliminary study was split into two phases, with Phase 1 ( $N=47$ ), ages 18 to 71 yrs ( $M=47.19$ ,  $SD=14.62$ ), assessing the relationship between HRQL and SWL with physical activity, as measured by MET hours per week and number of vigorous bouts of physical activity per week, and Phase 2 ( $N=9$ ), ages 41 to 71 yrs ( $M=55.33$ ,  $SD=9.77$ ), assessing HRQL and SWL with aerobic fitness, measured with a  $VO_2$  max test. In Phase 1, there was a statistically significant correlation ( $r=.70$ ) between bouts of vigorous physical activity and the HRQL composite. In Phase 2, moderate positive correlations were found for  $VO_2$  peak with the SF-36 aggregate physical component score. MET hours per week did not strongly predict HRQL or SWL in either phase. Additional

research is needed to explore why relationships are being found for vigorous bouts of activity and not MET hours per week. Further, a larger sample size is needed to test the relationship between VO<sub>2</sub> peak and HRQL, to determine what relationships emerge when the study has sufficient power.

### *Physical Activity, Aerobic Fitness, and Cognition*

#### *Overview*

The effects of aerobic fitness on cognitive function have been investigated in all age groups by correlation, cross-sectional and experimental design studies conducted in human and animal models. Although most cross-sectional data support the beneficial effect of aerobic fitness on cognition, intervention studies are more variable. Further, correlation and cross-sectional studies do not manipulate aerobic fitness; therefore, they cannot be interpreted exactly like findings from intervention studies, where aerobic fitness is manipulated (Etnier, Nowell, Landers, & Sibley, 2006).

Theories guiding research on aerobic fitness and cognition include the cardiovascular fitness hypothesis, the cognitive reserve hypothesis, and the executive control hypothesis. The cardiovascular fitness hypothesis predicts that aerobic fitness mediates the relationship between physical activity and the health benefits obtained (North, McCullagh, & Tran, 1990) and cognitive performance (Etnier, 2008). Another theory is the cognitive reserve hypothesis. Cognitive reserve is simply how the brain stays resilient to damage, while using what resources it has available in the most efficacious way possible. The hypothesis proposes that physical activity may provide more benefits for individuals with limited cognitive reserves (Chodzko-Zajko & Moore, 1994; Etnier & Landers, 1998). Finally, the executive control hypothesis states that

physical activity will benefit those tasks which require executive control (effortful processing) compared to those tasks which are automatic. Therefore, in addition to older adults who have limited cognitive reserves due to aging and/or age-related declines in executive control process, chronic disease populations with known neurological complications from their disease state might also benefit from physical activity.

For the purpose of this literature review, the focus will be on the executive control hypothesis and executive function tasks used to measure cognitive function. Executive function consists of capabilities, such as volition, initiation, planning, purposive action, self-monitoring, and self-regulation, which enable adults to act appropriately and independently (Lezak, Howieson, & Loring, 2004). Conceptually, executive function is one of the three dimensions of behavior, with executive function being how a behavior is expressed, and cognition and emotionality, being how information is handled, and feelings about this information, respectively (Lezak et al., 2004). Executive functions differ from cognitive functions in that they are a behavior that results from “how” or “whether” a person does something, versus “what” or “how much” a person does (Lezak et al., 2004). When executive functions are hampered, the ability to carry out cognitive tasks becomes compromised.

Executive function is associated with the frontal and parietal regions of the cortex (Kramer et al., 1999) and aerobic fitness has been shown to preserve the integrity and structure of the gray and white matter tracts in the frontal, parietal, and temporal cortices (Colcombe, Kramer, Erickson et al., 2004). Further, Colcombe et al.’s (2003) research on aerobic fitness and brain tissue loss is consistent with these findings in that aerobic

fitness spared cortical density loss in older adults in the gray matter in the frontal, temporal, and parietal lobes and in the white matter tissue in the anterior and posterior tracts.

### *Mechanisms*

A moderator and mediator are 3<sup>rd</sup> variables that might impact the relationship between the dependent and independent variables (Baron & Kenny, 1986). A moderator is categorical or continuous and affects the direction of the relationship, while a mediator (mechanism) exhibits indirect effects and is usually either a variable that represents a broad construct (mediator) or a more quantifiable construct (mechanism), such as number of neurons (Etnier, 2008). Etnier (2008) reported that moderators of the relationship between physical activity and cognition in older adults include age, gender, estrogen status, APO E-4 genotype and depression. Mediators or mechanisms can be detected with statistical tests and may be represented in a variety of causal chains (single and multiple micromediation). Further, mediators can be represented as psychological (quality of life, motivation), behavioral (eating patterns), disease state (type of disease), and physiological (hormones, neurotransmitters); however these mediating relationships are seldom tested (Etnier, 2008; Etnier et al., 2006).

Etnier et al. (1997) suggested three possible mediators or mechanisms, increased cerebral blood flow, increased neurotransmitters, and permanent structural changes in the brain, to explain the relationship between aerobic fitness and cognitive function. For example, the cerebral circulation hypothesis proposes that oxygen transport in the brain is enhanced with chronic exercise. This enhancement in oxygen transport may result in

better cognitive performance due to an increased availability of resources (Chodzko-Zajko & Moore, 1994).

Increased neurotransmitters, structural changes in the brain, and the impact of hormones on brain changes have been shown mostly through animal models. For example, aerobic training has been found to improve plasticity and neuronal survival through increases in brain-derived neurotrophin factor (BDNF) (Neeper, Gómez-Pinilla, Choi, & Cotman, 1995). Cotman and Engesser-Cesar (2002) used animal models to show that voluntary wheel running in rats increased mRNA for BDNF. BDNF has been found to increase levels of the proteins needed for neuronal synapses, which are needed for cognitive function, and is therefore an important component of neuronal communication. Cameron and McKay (1999) noted that cell proliferation rates can increase in aged animals if cortisol levels are decreased. Both animal studies (Berchtold, Kesslak, Pike, Adlard, & Cotman, 2001) and human studies (Erickson et al., 2006) suggest that estrogen might be an important predictor of the outcomes of aerobic fitness. For example, Colcombe et al. (2003) found that females who exercised and were on hormone replacement therapy (HRT) had a greater increase in cortical density than those not on HRT. Berchtold et al. (2001) found that the rate of BDNF transcriptions is increased in aged animals when estrogen is present.

Other hormones, human growth factor (HGF) and insulin-like growth factor (ILG-1), that are released during strength training may impact and heighten the effects of aerobic training in older adults, through their effects on neuronal growth, differentiation, and performance (Colcombe, Kramer, McAuley, Erickson, & Scalf, 2004).

## *Research*

The results of the correlational, cross sectional, prospective/retrospective, and intervention studies and those of the meta-analyses, although not specific to CD, are important as they help us understand how physical activity may impact cognitive function in CD patients. Further, symptoms/disease implicated in other populations studied, such as dementia in older adults or fatigue in FMS patients, are relevant when investigating how physical activity may impact cognition in CD patients. Finally, the literature also gives us information on which types of tests (physical activity, aerobic fitness and cognition) were valid and reliable and types of methodical issues that other researchers may have experienced. Therefore, meta-analytic reviews, literature reviews, correlation/cross-sectional, prospective/retrospective, and randomized controlled studies/trials that are relevant to CD will be discussed. These will include older adult and chronic disease populations and relevant prospective/retrospective studies.

*Meta-analyses.* Meta-analyses conducted in this area have focused on elderly persons with cognitive impairment (Heyn et al., 2004), healthy and sedentary older adults (Colcombe & Kramer, 2003), children (Sibley & Etnier, 2003), and across all ages (Etnier et al., 2006; Etnier et al., 1997). These meta-analyses consistently show that chronic physical activity positively impacts cognitive performance.

Based on previous experimental research in humans and animals, it was hypothesized by Etnier et al. (1997) that chronic training programs or cross-sectional designs that compared fit to unfit would have the largest effect sizes and that exercise would most benefit the mentally impaired and older adults who may be resource limited.

Exercise was categorized as acute, chronic, mixed, cross-sectional/correlational and 106 different cognitive assessments were used in the studies analyzed. The larger effect found for the cross-sectional / correlation exercise studies supports the first hypothesis, while the prediction that those with reduced mental ability would have larger effects was not supported in both the acute and chronic studies, since mental ability was not a significant moderator. When age group was assessed, it was not a significant moderator in the acute studies; however, it did significantly impact effect size in the chronic studies. However, the college age group had significantly larger effects than the oldest age group and therefore, the hypothesis that older adults might have larger effects was not supported. The overall effect sizes were .53 for cross-sectional/ correlation exercise, .33 for chronic exercise, and .16 for acute exercise. An overall effect size of .18 was reported for randomized experimental designs. These effect sizes are important as they help develop an approximation of the types of effects that could be found when investigating aerobic fitness in CD patients.

Colcombe and Kramer (2003) conducted a meta-analytic review and included healthy and sedentary older adults, with an average age of 55 years, from 18 intervention studies. Cognitive processes were categorized according to four theoretical areas, speed, visuospatial, controlled processing, and executive control. Exercise was found to have the greatest effect on executive processes ( $ES = .68$ ), and combined strength and aerobic training were better than aerobic training alone (.59 vs. .41). Long duration training programs had the largest effect (.67), while both moderate bouts and long bouts both had significant effects (.61 and .47). Age moderated the relationship in that the 66 to 70 year

olds experienced the largest benefits. Finally, groups that contained greater than 50% females had larger benefits than those with less than 50% females. Participant characteristics, type of training, and type of cognitive task did not impact the effect size. Also, when changes in VO<sub>2</sub> max were categorized (no change, 5-11% change, and 12-25% change) and assessed, effect sizes were not significantly altered based on these VO<sub>2</sub> levels.

Heyn et al. (2004) conducted a meta-analysis that focused on older adults (greater than 65 years of age) with cognitive impairment and dementia. Dementia has been implicated in CD patients, so it is helpful to assess the results of this meta-analysis. Thirty randomized trials (72% women) were assessed and the overall mean effect size was 0.62. Cognitive performance effects were 0.57. Heyn et al.'s (2004) meta-analysis had limitations, including the inclusion of studies with a small sample size, lack of blinding procedures, and lack of clarity if exercise intensity was maintained throughout the study. Although criticized, it still sheds light on the potential impact of exercise training on the elderly with dementia.

The purpose of Etnier et al.'s (2006) meta-regression analysis was to statistically examine the relationship between aerobic fitness and cognitive performance using regression techniques that assess dose-response or the degree of influence of aerobic fitness on cognitive performance. An overall effect size of 0.34 was found for cognitive performance. In the cross-sectional and pre-post studies, age interacted with aerobic fitness. No relationships between aerobic fitness and cognitive performance were found for the cross-sectional and post-test studies; however, a negative relationship was found

in the pre-post studies. Only the correlation studies provided a positive effect ( $r=0.29$ ). Overall, results of the meta-regression were not found to support the cardiovascular fitness hypothesis. Etnier et al. (2006) concluded that other factors need to be explored, in that aerobic fitness may not predict cognitive performance or may only partially predict it. Possible explanations were given to explain why aerobic fitness did not predict cognitive function. It was thought that maybe aerobic fitness is not a precise enough measure and therefore cannot capture all of the physiological changes that occur in response to chronic exercise.

*Randomized controlled trials.* While there are many randomized controlled trials which show the benefits of aerobic exercise on cognition, Colcombe et al. (2004) is of particular interest since the research design employs older adults, the Rockport 1-mile walk, and cognitive testing that assesses executive function. Colcombe et al. (2004) investigated cortical plasticity in two studies, a cross-sectional assessment and a randomized clinical trial.  $VO_2$  max was estimated based on the participants' performances in the Rockport 1-mile walk test. Cognitive testing was conducted using the Erickson Flankers Task and functional magnetic resonance imaging (fMRI) was used to assess cerebral activity during task performance. In the randomized controlled trial, 29 participants completed the Erickson Flankers Task 1-week pre-intervention and 1-week post-intervention. The participants were randomly assigned to one of two groups for 6-weeks, either the aerobic group or the stretching and toning group (control). Results of the randomized controlled trial showed that the aerobic group increased their cardiovascular fitness by 10.2%, while the control group only increased by 2.9%.

Although the Erickson Flanker Test results were not significant, the aerobic group experienced an 11% decrease in interference, while the control group only experienced a 2% decrease in interference. The fMRI results for the randomized controlled trial indicated that the aerobic group had greater activation in areas associated with attention (Colcombe, Kramer, Erickson et al., 2004). Finally, when the aerobic group was compared to the control, there was significantly less activity in the anterior cingulate cortex (ACC) (Colcombe, Kramer, Erickson et al., 2004).

*Cross Sectional.* The investigation by Colcombe, Erickson, Raz, Webb, Cohen, McAuley et al. (2003) is important since it examined the effects of cardiovascular fitness on cortical density in older adults aged 55-79 years. Loss of white matter density has been implicated in CD patients; therefore, this study informs of the beneficial effects of aerobic fitness on this brain area. This cross-sectional study examined the gray and white matter tracts and found fitness was a significant moderator of cortical tissue loss. The areas most affected were gray matter in the frontal, temporal, and parietal lobes and white matter tissue in the anterior and posterior tracts (Colcombe et al., 2003).

The research design in Colcombe et al. (2004) helps inform the current research study since it uses the Rockport 1-mile walk and executive function tests. In Colcombe et al (2004), cortical plasticity was investigated in two studies, a cross-sectional assessment and randomized clinical trial. In the cross sectional assessment, 41 older adults completed the Rockport 1-mile walk test, and cognitive testing using the Erickson Flankers Task and fMRI. Participants were split (high fit, low fit) based on the median of their estimate VO<sub>2</sub> max test, derived from the Rockport 1-mile walk test. The results of

the Erickson Flanker's task showed that high fit older individuals performed better with the conflict cues ( i.e., reduction in behavioral conflict) than the low fit older adults, while the fMRI showed that high fit older adults had greater effective attentional control (Colcombe, Kramer, Erickson et al., 2004).

*Prospective and retrospective.* In addition to cross-sectional and correlational studies, prospective and retrospective designs have been used to assess cognitive function; however, physical activity and not aerobic fitness is typically assessed. In prospective studies, physical activity is measured and then the participants are followed over months or years to determine if changes in cognition occur with time. Retrospective studies are designed to measure current cognitive function and then look back in time to assess physical activity levels.

Of the prospective studies that have examined cognitive performance outcomes, most support the beneficial effect of physical activity on cognition (Albert et al., 1995; Barnes, Yaffe, Satariano, & Tager, 2003; Dik, Deeg, Visser, & Jonker, 2003; Lytle, Vander Bilt, Pandav, Dodge, & Ganguli, 2004; van Gelder et al., 2004). Dik et al. (2003) was the only prospective study with cognitive performance outcomes that failed to support the benefit of physical activity on cognitive performance. This lack of support was likely due to their physical activity measure, which asked participants ( $n=1,240$ ) to recall physical activity from 50 years earlier and then used to measure and predict future changes in cognition. Lytle et al. (2004) used a self-report measure (three levels of exercise) and found strong support for high exercise level ( $\geq 30$  minutes;  $\geq 3$ x/week) being protective against cognitive decline. Yaffe, Barnes, Nevitt, Lui, and Covinsky

(2001), also used a self-report measure, but assessed total kilocalories of energy expended per week as their measure, instead of exercise level. The authors found that compared to the lowest quartile, the highest quartile had a 35-37% less risk of cognitive decline. Further, for every 1700 kcal of energy expended, there was a 14% less risk of decline. In the prospective studies that measured clinical outcomes, such as dementia risk (Abbott et al., 2004; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), cognitive function in nurses (Weuve et al., 2004) and Alzheimer's Disease (AD) (Lindsay et al., 2002; Wilson et al., 2002), all but Wilson et al. (2002) showed support for the benefits of physical activity. The studies that supported a relationship generally found physical activity to be positively related to cognition and negatively related to disease risk. Wilson et al. (2002) did not find physical activity level (weekly hours of physical activity) to be related to AD risk. However, this might be due to the failure to assess disease magnitude/status at baseline and the failure to assess past cognitive activities, which would more likely be associated with a decreased risk of AD than current cognitive activities.

### *Summary*

CD is an autoimmune condition, which is triggered by ingestion of gluten, and requires lifelong adherence to the GF diet to minimize symptoms. Those with CD have been found to experience lower levels of HRQL than the general population, even when adhering to the GF diet. Neurological studies have reported brain atrophy and dementia, both of which affect executive function. There are few behavioral studies that have used cognitive tests to assess executive function in CD patients. Physical activity has been

investigated in other chronic disease populations and has been shown to be positively predictive of HRQL and cognition in cross-sectional studies, and influential on HRQL and cognition in experimental studies. However, the results for aerobic fitness are mixed in that aerobic fitness has not always impacted HRQL or cognition in experimental designs. This may indicate that changes in aerobic fitness are not necessarily the mechanism driving the changes in HRQL or cognition. There are not any studies to date that have investigated how physical activity and aerobic fitness are related to HRQL and executive function in CD patients; therefore, knowing that cognition may be improved in other populations studied (chronic disease, older adults) as a result of physical activity, and in some cases, aerobic fitness, supports the need for a research study that investigates how both physical activity (self-report) and aerobic fitness (estimated from a submaximal test) relate to executive function in CD patients.

## CHAPTER III

### PILOT STUDY

#### *Purpose*

The purpose of this section is to describe pilot work that was conducted on the relationship of physical activity and aerobic fitness with HRQL, satisfaction with life, and depression. The results of this pilot study were used to inform the methods used in the current study,

#### *Hypotheses*

In Phase 1 of the pilot study, relationships between physical activity and psychological variables were assessed. It was hypothesized that higher physical activity (MET hours/week and number of vigorous bouts of physical activity/week) would be associated with higher HRQL and SWL and lower depression. In Phase 2, aerobic fitness was assessed in a smaller sample to provide exploratory evidence regarding the potentially differential effects of physical activity (the behavior) and aerobic fitness (the physiological response to regular moderate physical activity) on the psychological outcome variables. It was hypothesized that higher aerobic fitness would be associated with higher HRQL and SWL and lower depression.

#### *Participants*

In Phase 1, community-dwelling adults with CD, were identified and recruited to participate in the study through local and national CD support groups, an advertisement

on the Gluten Intolerance Group website, local newspapers, presentations at support group meetings, and flyers posted at local health food stores. The researchers asked that all participants be biopsy-diagnosed with CD by a medical doctor; however 5 of the 47 who completed Phase 1 of the research study had only been diagnosed by blood tests. Although, an intestinal biopsy is the gold standard for CD diagnosis (Green et al., 2001), sensitivity and specificity for blood test can range between 53-100% and 42-100%, respectively. Therefore, results were examined with and without these five participants. Results did not differ when these participants were excluded from the analyses; therefore, these 5 participants were included in all statistical analyses and all results are presented with these 5 participants included.

Participants in Phase 1 received a hard copy of the survey packet by mail or in person, and were asked to complete the survey at home and to return it to the principal investigator in the self-addressed stamped envelope. Sixty-five surveys were given out and 47 were returned for a response rate of 72%.

In Phase 2, the participants were identified and recruited to participate through the participant pool in Phase 1 and through the same methods as described in Phase 1. In the Phase 1 surveys, participants were asked if they wanted to participate in Phase 2. If they indicated yes ( $N=17$ ), then they were recruited for Phase 2. These participants were screened according to the guidelines of the American College of Sports Medicine (American College of Sports Medicine, 2006) and using the Physical Activity Readiness Questionnaire (PARQ). To qualify for the study, participants had to be healthy enough to perform a maximum exercise bout on the treadmill. Six of the 17 from Phase 1 who

volunteered to participate in Phase 2 met the inclusion criteria. Six new participants were recruited by the same means used in Phase 1 for an initial total of 12 participants. Three of the participants were dropped from the analyses due to incomplete data, for a total of 9 participants in Phase 2.

### *Materials*

The survey packet used in both phases consisted of six questionnaires. The first questionnaire, General Health and Demographics Questionnaire, was developed by the principal investigator, and was used to obtain information about CD diagnosis, GF diet, and demographics. HRQL was measured using the Medical Outcomes Study Health Survey, the Short Form 36 (SF-36) (Ware & Sherbourne, 1992) and the Health and Well-being Ratings (HWB) (Gill et al., 1997; King et al., 1989). SWL was measured using the Satisfaction with Life Scale (Diener, Emmons, Larsen, & Griffin, 1985). Depression was measured with the Beck Depression Inventory II (Beck, Steer, & Brown, 1996). Physical activity was measured using the Aerobics Center Longitudinal Study Physical Activity Questionnaire (Kohl, Blair, Paffenbarger Jr., Macera, & Kronenfeld, 1988). All surveys have well-established and acceptable psychometrics, except the HWB ratings, which are single items with no psychometrics reported.

MET hours/week were determined using The Compendium of Physical Activities Tracking Guide (Ainsworth, 2002; Ainsworth et al., 2000), which assigns MET values to activities based on duration, intensity, time and type of physical activity in three areas: exercise, household activities, and lawn/gardening activities. Number of vigorous bouts of physical activity/week was determined by the response to question #2 on the survey,

“How many times a week do you engage in vigorous physical activity long enough to work up a sweat? \_\_\_\_\_(times per week)” One subject answered, “sometimes” and that data was not included in the analysis.

In Phase 2, the PARQ was used to assess whether or not the participant met the inclusion criteria. If approved to participate, participants were asked to avoid consumption of caffeine and exposure to second hand cigarette smoke three hours prior to their laboratory visit. It was also requested that they not exercise on the day of their testing and only participate in light to moderate exercise two days before their testing.

#### *Procedures*

In Phase 1, participants completed the surveys at home and returned them to the principal investigator in the self-addressed stamped envelope.

In Phase 2, informed consent was obtained upon arrival to the University. This pilot study was approved by the Institutional Review Board at the University. Each participant completed the surveys within one week of completion of the VO<sub>2</sub> max test. A Quinton TM65 Treadmill equipped with safety rails, a Quinton Q-stress EKG system, a Sensormedics VS 29c Cardiopulmonary Exercise metabolic cart, and Polar Heart Rate monitors were used during the aerobic fitness test. Weight was obtained through self-report. Participants were given directions and information about the aerobic fitness test and then moved to the treadmill for the VO<sub>2</sub> max test. Next, EKG electrodes, the Polar Heart rate monitor, and the head gear and face mask were put on the participant. A physician was present for all testing. The Astrand protocol was used and at the end of each stage, perceived exertion was measured using the Borg Rating of Perceived Exertion Scale

(Borg, 1998). Participants reached their VO<sub>2</sub> peak within 9-14 minutes. VO<sub>2</sub> max was considered to have been achieved if a plateau in VO<sub>2</sub> occurred with an increase in workload or if the following two criteria were met: 1) a respiratory exchange ratio at test termination of >1.15, or 2) a heart rate (HR) at test termination > 90% of age-predicted maximal heart rate (220-age). Not all subjects were considered to have reached VO<sub>2</sub> max, according to the criteria; therefore, the measure of aerobic fitness is most accurately described as VO<sub>2</sub> peak. The testing was done following the guidelines of the American College of Sports Medicine (American College of Sports Medicine, 2006). After completion of the test, the treadmill was lowered to 0% grade and the speed reduced to 2.0 mph and participants continued to walk to cool down for  $\geq 5$  minutes. HR was monitored to ensure that the value stabilized before the participant was permitted to leave the laboratory.

Twelve subjects were tested during Phase 2; however, only data for nine subjects are included. One subject did not complete the surveys, one subject stopped the test due to feeling claustrophobic with the face mask gear, and one subject's data was not saved properly.

#### *Statistical Analyses*

To analyze the Phase 1 HRQL data, a linear composite of the eight SF-36 subscales and the HWB score was created using canonical correlations. Separate canonical correlations were conducted for each measure of physical activity (MET hours/week, bouts of vigorous physical activity/week). Bivariate correlations were conducted to examine relationships between the physical activity measures and

depression and SWL. A Bonferroni correction was used because four separate analyses were conducted; thus, correlations were considered significant if  $p < .013$ .

In Phase 1, additional bivariate correlations were conducted to explore the relationships between the two physical activity variables (MET hours/week and bouts of vigorous physical activity/week) with the individual subscales of the SF-36 and the HWB rating. The purpose was to identify the directions of the relationships on an exploratory basis, and no significance tests were conducted.

Finally, for Phase 1, the sample data was compared to normative data and/or interpretation scales from healthy populations for the SF-36 measures, Satisfaction with Life, Health and Well-Being ratings, BDI-II, and physical activity.

The small sample size ( $N=9$ ) for the Phase 2 data did not allow canonical correlations to be conducted; therefore, bivariate correlations were conducted for  $VO_2$  peak with depression, HRQL (all SF-36 subscales and HWB score) and SWL. Significance was tested; however, because Phase 2 is exploratory, corrections for multiple tests were not made. The strength of the correlations and effect sizes are reported. Finally, for Phase 2, the sample data was compared to normative data on aerobic fitness.

*Results: Phase 1*

Age, biopsy status, gender, and GF diet adherence information for 47 CD patients aged 18 to 71 yrs ( $M=47.19$ ,  $SD=14.62$ ) is presented in Table 2. Descriptive statistics for all variables are presented in Table 3.

Table 2  
*Age, Biopsy Status, Gender, GF Diet Adherence Information and Mean Vigorous Bouts of Physical Activity/Week, MET Hours/Week, and VO<sub>2</sub> Peak*

Participation	Phase	
	Phase 1 (N)	Phase 2 (N)
N	47	9
Male	10	2
Female	37	7
Biopsy/Endoscopy Diagnosis	42	9
Yes to GF Diet Adherence Within Past 2-weeks	45	9
100% Adherence	30	3
90% Adherence	15	5
75% Adherence	2	1

Measure of variable	Phase 1	Phase 2
	M(SD)	M(SD)
Age	47 (14.62)	55 (9.77)
Vigorous Bouts of Physical Activity/Week	3.35 (2.60)	2.94 (2.31)
MET hours/week	51.74 (33.91)	75.38 (46.06)
VO <sub>2</sub> max	n/a	29.97 (10.06)
Median VO <sub>2</sub> max	n/a	25.90 (10.06)

Table 3  
*Phase 1 Means (Standard Deviations) for Physical Activity, HRQL, and Mental Health Measures*

Variables	N <sup>a</sup>	Mean	Standard Deviation
Category A			
MET hours/week	47	51.74	33.91
Vigorous Bouts of PA/week	46	3.35	2.60
SF-36 Physical Functioning	46	50.12	8.68
SF-36 Role Personal	47	46.64	11.65
SF-36 Bodily Pain	47	48.05	11.16
SF-36 General Health	47	46.45	11.18
SF-36 Vitality	47	48.30	11.50
SF-36 Social Functioning	46	45.94	11.27
SF-36 Role Emotion	45	47.76	12.48
SF-36 Mental Health	47	48.15	11.58
SF-36 Physical Component Score	46	48.92	9.84
SF-36 Mental Component Score	46	46.83	13.33
Health and Well-Being Rating	47	22.09	4.88
Satisfaction with Life Scale	47	23.15	8.33
BDI-II*	47	10.64	8.93

*Note.* \*higher score is worse (i.e. more depression). <sup>a</sup> indicates a difference in N's are due to incomplete data

*Relationships between physical activity variables and psychological variables*

The correlation between bouts of vigorous physical activity/week and the HRQL (SF-36 & HWB) composite was statistically significant ( $R_c=.70$ ). For MET hours/week, there was a moderate positive correlation that was not statistically significant ( $R_c=.37$ ).

The moderate, positive correlation ( $r=.32$ ) between bouts of vigorous physical activity/week and SWLS was not statistically significant after a Bonferroni correction, and MET hours/week was not related to SWL.

No significant relationships were found for bouts of vigorous physical activity/week or MET hours/week with depression.

The correlations for the Phase 1 bivariate correlations between physical activity variables and SF-36 subscales and HWB rating are presented in Table 4. These bivariate correlations were conducted for exploratory purposes and significance was not considered. There was a moderate positive correlation ( $r=.36$ ) between MET hours/week and bouts of vigorous physical activity/week.

MET hours/week was not strongly related ( $r<.20$ ) to any of the HRQL variables or SWLS. However, bouts of vigorous physical activity/week were moderately positively related to SF-36 physical functioning ( $r=.53$ ), SF-36 role personal ( $r=.51$ ), and HWB ratings ( $r=.46$ ).

Table 4  
*Correlations for Measures of Physical Activity and Aerobic Fitness with Psychological Outcomes*

Variables	MET hours/week (n=47)	Vigorous PA/week (n=46)	VO2 peak (n=9)
Category A			
SF-36 Physical Functioning	.01	.53	.14
SF-36 Role Personal	.00	.51	.23
SF-36 Bodily Pain	-.10	.36	-.13
SF-36 General Health	-.05	.28	.23
SF-36 Vitality	-.06	.38	-.47
SF-36 Social Functioning	-.16	.26	.34
SF-36 Role Emotion	.06	.37	-.12
SF-36 Mental Health	-.08	.21	-.89
SF-36 Physical Component Score	-.06	.40	.40
SF-36 Mental Component Score	-.04	.26	-.58
Health and Well-Being Rating	.20	.46	.12
Satisfaction with Life Scale	-.06	.32	-.20
BDI-II*	.16	-.15	.55

*Note.* \* higher score is worse (i.e. more depression).

*Normative data*

When compared to normative data on the psychological variables, the CD sample had very slightly lower HRQL, as measured by the SF-36 and HWB ratings, similar levels of SWL and lower depression.

The American College of Sports Medicine recommends that healthy adults, ages 18 to 65 years participate in moderate intensity physical activity for at least 30 minutes, 5 days per week or vigorous physical activity at least 20 minutes on 3 days per week (Haskell et al., 2007). This recommendation equates to a MET expenditure of between 450 to 750 MET minutes per week or 7.5 to 12.5 MET hours per week (Haskell et al., 2007). In 2007, the Centers for Disease Control and Prevention (Centers for Disease

Control and Prevention, 2007) reported that only 48.8% of men and women met the above recommendation. The Phase 1 sample completed an average of 3.35 vigorous bouts of physical activity/week. This sample also participated in a mean of 53 MET hours per week; however, this MET hour calculation included exercise, household activities, and gardening.

### *Results: Phase 2*

Community-dwelling biopsy diagnosed adults ( $N=9$ ), ages 41 to 71 yrs ( $M=55.33$ ,  $SD=9.77$ ), participated. Age, biopsy status, gender, and GF diet adherence information is presented in Table 1. The mean  $VO_2$  peak for the 7 female participants was 27.26 ml/kg/min (range 21.6-37.2), while the mean  $VO_2$  peak for the 2 male participants was 39.45 ml/kg/min (range 25.9-53.0).

#### *Relationships between $VO_2$ peak and the psychological variable*

$VO_2$  peak was significantly related to SF-36 mental health ( $r=-.89$ ,  $p=.001$ ), indicating that as  $VO_2$  peak increases, mental health decreases.

The correlations and effect sizes for the exploratory bivariate correlations between  $VO_2$  peak and all psychological variables are presented in Table 3

$VO_2$  peak was moderately positively correlated with the SF-36 aggregate physical component score ( $r=.40$ ), and moderately negatively correlated with SF-36 vitality ( $r=-.47$ ), and the aggregate SF-36 mental component score ( $r=-.58$ ).

$VO_2$  peak was not related to SWL.  $VO_2$  peak was a moderate predictor of depression ( $r=.55$ ), indicating that as  $VO_2$  peak increases, depression increases.

### *Normative data*

When compared to normative data on aerobic fitness, the Phase 2 sample was very similar in terms of VO<sub>2</sub> max for men ( $M=37.6$ ,  $SD=3.8$ ) and women ( $M=29.3$ ,  $SD=3.6$ ) in the moderate fitness category ( $N=3837$  men;  $N=1110$  women), as reported in the Aerobics Center Longitudinal Study (Stofan, DiPietro, Davis, Kohl III, & Blair, 1998).

### *Discussion*

The purpose of this pilot study was to determine if physical activity and aerobic fitness were related to HRQL, SWL and depression in CD patients. In Phase 1, a self-report physical activity scale was used to assess MET hours/week and number of vigorous bouts of physical activity/week. In Phase 2, a VO<sub>2</sub> max test was used to assess aerobic fitness. Given the literature supporting a need to investigate HRQL and depression in CD patients, and the beneficial effects of physical activity in other disease state populations and in healthy populations, the primary purpose was to determine if physical activity could have similar beneficial effects in CD patients. The study is exploratory in nature and limited in scope, but provides preliminary data on the relationships between physical activity and psychological outcome variables to guide continuing research.

The findings in Phase 1 confirmed the prediction that vigorous bouts of physical activity/week were related to HRQL. However, vigorous bouts of physical activity/week were not predictive of depression. Further, MET hours per week were not significantly related to any of the mental health or HRQL variables.

The findings in Phase 1 show that vigorous bouts of physical activity/week, but not MET hours, predicted the psychological variables. It was hypothesized that both physical activity measures would predict HRQL and mental health; therefore, these mixed results were unexpected. One likely explanation for these results is related to the method of measuring physical activity. Physical activity was measured as the number of vigorous bouts of physical activity/week reported and MET hours/week calculated based upon the reported activities, durations, and intensities. It is likely that participants are more able to accurately recall the number of vigorous bouts of physical activity/week performed than the details necessary to accurately calculate MET hours/week. This conclusion is supported by the findings of several researchers. Relative validity is greater when assessing vigorous activity than when assessing moderate activity in adults (Sallis & Saelens, 2000). It has also been reported that lower reliability coefficients were found for household activities recalled from generic memory than for specific exercise bouts recalled from episodic memory (DiPietro, Caspersen, Ostfeld, & Nadel, 1993).

Contextual cues may be present to help a responder identify exercise bouts; however, less structured daily activities, of light to moderate intensity, may be reported less due to lack of contextual cues (Matthews, 2002). Thus, the significant relationships for vigorous bouts of physical activity/week, which measure only vigorous activity, might be indicative of less measurement error as compared to MET hours/week, which measures exercise, household, and garden activities with varying intensities.

Depression and mood were also outcome variables in Phase 1 that were hypothesized to be positively associated with physical activity; however our data did not

show vigorous bouts of physical activity/week or MET hours/week to be significantly related to these outcomes. Further, it is unclear why vigorous bouts of physical activity/week and MET hours/week were generally not predictive of depression. There is evidence that physical activity is most important for people who have increased depression. For example, meta-analytic reviews have shown larger effects of physical activity on depression for moderately to severe clinically depressed populations as compared to mild to moderate depressed populations (Craft & Landers, 1998) and for those participants who were initially unhealthy, both physically and psychologically (North et al., 1990). Given that this CD sample was less depressed than the general population, it might be that physical activity was not related to depression because this sample was not depressed.

In Phase 2, moderate positive correlations were found for VO<sub>2</sub> peak with the SF-36 aggregate physical component score; however, other findings in Phase 2 indicated that VO<sub>2</sub> peak was negatively associated with other psychological outcomes (i.e. SF-36 mental, BDI-II), meaning that as VO<sub>2</sub> peak increased, mental HRQL and depression worsened. These negative findings were unexpected, but are likely due to the small sample which might have precluded the ability to observe significant relationships.

In conclusion, although the results of this study were not consistently supportive of a beneficial relationship between physical activity and psychological outcomes in CD patients, there were some findings that suggest that future study is warranted. In particular, in this sample of CD patients, who were not experiencing psychological distress relative to population norms, there was a consistent positive relationship between

vigorous bouts of physical activity/week and all of the psychological measures. That is, CD patients who performed more vigorous bouts of physical activity/week reported better HRQL and better satisfaction with life than did those who participated in less vigorous bouts of physical activity/week. These results were not corroborated by the METs data or by the VO<sub>2</sub> peak data. However, the METs data is likely to be less reliable given the measurement issues associated with this data. Further, the VO<sub>2</sub> peak data came from only 9 participants suggesting that future research will be needed to explore the role of fitness in potential relationships between physical activity and psychological outcomes.

## CHAPTER IV

### METHODS

#### *Participants*

A total of 47 community dwelling men and women between the ages of 24 to 70 years with CD were recruited to participate in the study.

CD patients were recruited from local CD support group chapters. The following chapters in North Carolina (NC) were contacted: NC Piedmont Triad Gluten Intolerance Group in Winston Salem, NC, Triangle Gluten Intolerance Group in Durham, NC, Asheville Gluten Intolerance Group, in Asheville, NC, Celiac Support Group in Charlotte, NC. Other chapters in Virginia, South Carolina, California, Florida, and Pennsylvania were contacted to ensure that there were enough participants.

Further, newspaper advertisements (News and Record, Greensboro, NC), newsletter inserts (CD newsletters), and flyer postings were used. Flyers were posted in local health food stores, such as Whole Foods, Earthfare, Trader Joe's and Deep Roots Market. Also, an advertisement for the study was posted on the Gluten Intolerance Group website ([www.gluten.net](http://www.gluten.net)), on the Celiac.com "Celiac Disease - Gluten Free" message board ([www.celiac.com](http://www.celiac.com)), on the Celiac Chicks website, ([celiacchicks.typepad.com](http://celiacchicks.typepad.com)) and on craigslist ([craigslist.org](http://craigslist.org)) in the volunteer section. Participants contacted the principle investigator via phone or email in response to the advertisement. An introductory letter was then emailed or U.S. mailed to the participants. See Figure 1 for a summary of the recruitment process.

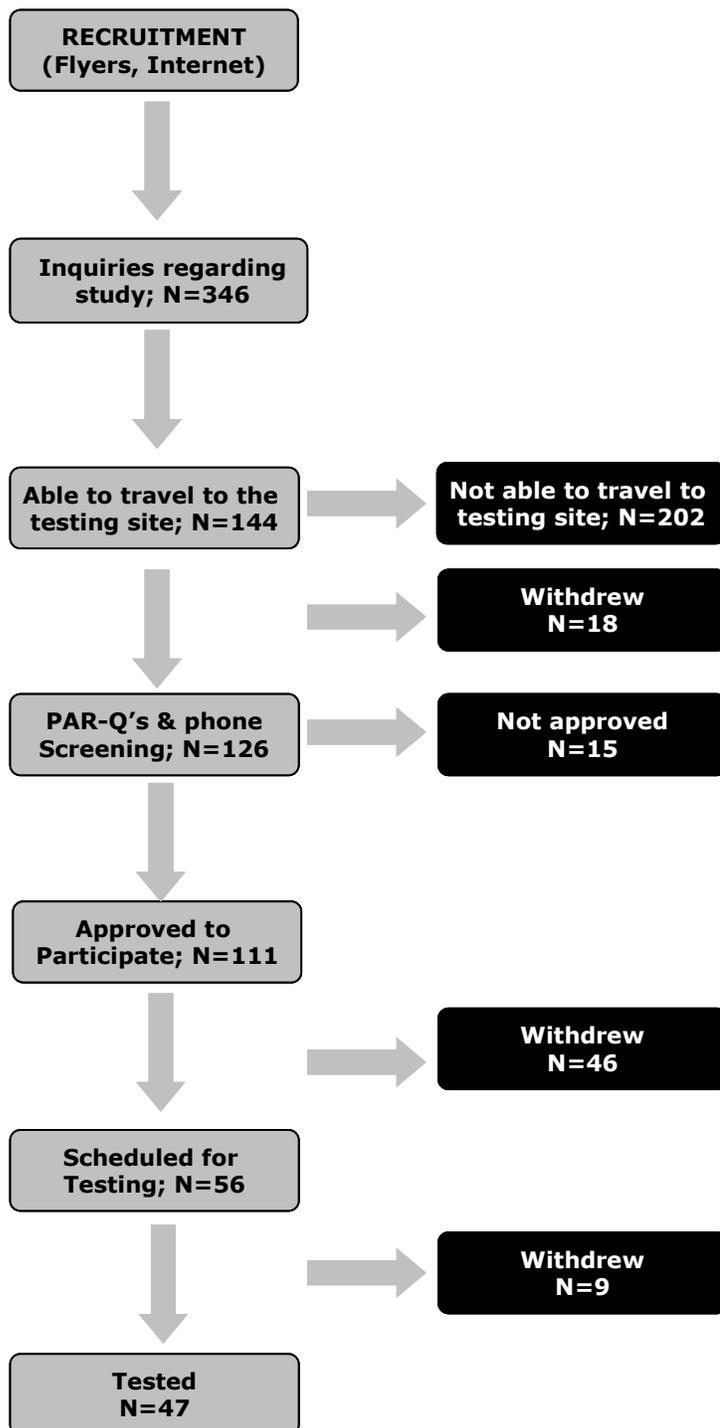


Figure 1. Recruitment process

### *Characteristics of this CD sample*

The mean age of this sample was 49 years ( $SD= 12.54$ ) and 72% of the participants were women. The percent of female participants is similar to that of other studies (Ciacci et al., 1995; Green, 2005; Green et al., 2001) and the pilot study (see Table 5). As with the pilot sample, data indicated that this CD sample also scored higher than population norms on physical activity levels (i.e. number of vigorous bouts per week and MET hours per week) and HRQL. This sample also scored higher than population norms on most executive function tests. Further, GF diet adherence in this sample was at 100% for all participants. Reasons for this above average HRQL, excellent diet adherence, and high levels of physical activity could be a result of the recruitment methods used in this study. A majority of the participants in the sample were members of a local or national support group. Thus, these CD patients appear to be using problem-focused coping and therefore might have different characteristics than those who are not members of a support group.

A summary of these normative comparisons is presented in Table 6; however, a more detailed description of the normative comparisons can be found in the results section.

Table 5  
*Pilot Study and Dissertation Study Sample Characteristics*

<b>Participation</b>	<b>Sample</b>	
	<b>Pilot (N)</b>	<b>Dissertation (N)</b>
N	47	47
Male	10	13
Female	37	34
Biopsy/Endoscopy Diagnosis	42	39
Yes to GF Diet Adherence Within Past 2-weeks	45	47
100% Adherence	30	43
90% Adherence	15	4
75% Adherence	2	0

Table 6  
*Summary of CD Sample Compared to Normative Values for Predictors and Criterion*

<b>Variables</b>	<b>Dissertation Sample Compared to Normative Group</b>
Vigorous Bouts	Better than
MET Hours	Better than
VO <sub>2</sub> max	Better than
SF-36	Better than
CDQ	Better than
MMSE*	Same or Slightly Better
Trail Making Test*	75% percentile
Digits Backward	Better than
Verbal Fluency*	Same or Slightly Worse
The CLOX Test	Better than

*Note.* \* relationship changes slightly based on age grouping and/or education level

### *Inclusion and Exclusion Criteria*

The goal of the inclusion criteria was to include all CD patients who were willing and able to complete the study and who could safely complete a submaximal aerobic fitness test. Participants were included or excluded based on their answers to the questions asked on the Physical Activity Readiness Questionnaire (PARQ). Exclusion criteria included conditions that would preclude performance of the submaximal aerobic fitness test (including a risk assessment as identified on the PARQ), functional limitations (i.e., could not walk 1-mile), use of medications that would suppress blood pressure or heart rate during the submaximal test, severe symptomatic heart disease), the consumption of psychotropic drugs, and inability to speak or write English.

### *Risk Assessment*

Risk was assessed based on information obtained in the PARQ. According to Table 2-4, American College of Sports Medicine Risk Stratification Categories, participants were stratified into one of three risk categories. Low risk was defined as men less than 45 years of age and women less than 55 years of age who were asymptomatic and met no more than one risk factor threshold from Table 2-2 (PARQ) (American College of Sports Medicine, 2006). Those in this low risk category were immediately invited to participate. Moderate risk was defined as men greater than or equal to 45 years and women greater than or equal to 55 years or those younger adults who met the threshold for two or more risk factors from Table 2-2 (American College of Sports Medicine, 2006). Those in this moderate risk category needed physician approval prior to completing the study. High risk was defined as individuals with one or more signs and

symptoms listed in Table 2-3 or known cardiovascular, pulmonary, or metabolic disease (American College of Sports Medicine, 2006) Those in this high risk category were excluded from the study.

### *Materials*

#### *Assessment of Potential Covariates*

Potential covariates that were available for inclusion as predictors in the regression model were: age (in years), gender (male, female), diet adherence rate perception (the subjects' self-report measure of their perceived % GF diet adherence over the last 2 weeks), diagnosis type (biopsy, blood, other, none), age at diagnosis, general cognition (MMSE score), and degree of satisfaction with information provided by doctors (level of satisfaction on a 5 point scale; score for diagnosis doctor and current doctor). Scores for these variables can be found in Table 7.

Table 7  
*Potential Covariates*

<b>Covariate Measures</b>	<b>Scores/Variables</b>
Age	In years (continuous variable)
Gender	0 = female; 1 = male
Diet Adherence Rate Perception	0 = 100%; 1=90%; 2=75%; 3=50%; 4=25%; 5=0%; Collapsed to 2 variables (0,1)
Diagnosis Type	Biopsy/Endoscopy of small intestine = 0; Blood test = 1; Dermatitis herpetiformis /Skin Biopsy = 2; Capsule Endoscopy = 3; Other = 4 Collapsed to 2 variables (0. 1)
Age at Diagnosis	In months (continuous)
General Cognition	Mini Mental State Exam score (continuous)
Degree of Satisfaction with Information Provided by Doctors	2 scores (diagnosis doctor; current doctor) based on the following scale: Not at all (1); slightly (2); moderately (3); quite a bit (4); extremely (5); Dummy coded into 4 variables

Diet adherence rate, age at diagnosis, and satisfaction with information provided by doctors were found to be influential in prior literature that assessed HRQL using both the SF-36 and Celiac Disease Questionnaire (CDQ) (Häuser, Gold, Stallmach, Caspary, & Stein, 2007) Age, gender, and general cognitive ability have been found to impact cognitive performance (Etnier & Landers, 1997; Etnier et al., 2006). These variables were assessed at entry into the study through the general demographics and health questionnaire and the MMSE.

### *Assessment of Independent (Predictor) Variables*

*Physical activity level.* The Aerobics Center Longitudinal Study Physical Activity Questionnaire measured self-reported level of physical activity (Kohl, Blair, Paffenbarger, Macera, & Kronenfeld, 1997). Validity correlations for treadmill time with run workouts ( $r=.35$ ) and treadmill time with frequency of sweating ( $r=.51$ ) ( $N=374$ ) were reported from the survey (Kohl et al., 1988). Oliveria, Kohl, Trichopoulos III, and Blair (1996) reported correlation coefficients of  $r=.41$  for maximal exercise treadmill time with weekly energy expenditure from physical activity for baseline physical activity, and  $r=.32$  for follow-up physical activity ( $N=7570$ ). Based on the pilot study, additional questions were asked so that the PI could better assess the intensity of some of the exercises, as well as differentiate between types of exercise (i.e. walking on a treadmill versus walking outside; mountain biking versus road cycling). These additional questions insured that MET values could be accurately calculated, from the Compendium of Physical Activities Tracking Guide (Ainsworth, 2002; Ainsworth et al., 2000), based on the participant responses in three areas: exercise, household activities, and lawn/gardening activities (see Table 8). If MET hours per week could not be accurately calculated, due to confusing or incomplete data, then total minutes of exercise was calculated. Number of vigorous bouts of physical activity per week were determined by the response to question #2 on the survey, “How many times a week do you engage in vigorous physical activity long enough to work up a sweat? \_\_\_\_ (times per week)” (see Table 8). This survey took 10-15 minutes to complete.

*Functional fitness test.* The Timed “Up and Go” Test (TUG) (Podsiadlo & Richardson, 1991) was used to assess functional mobility. While being timed, seated participants rose from a chair with arm rests, walked 3 meters as quickly as possible, turned 180 degrees, returned to the chair, and sat down. One practice trial was given. The participant was scored based on the average time it took to complete two real trials. Inter-rater reliability has been reported as 0.99, while intra-rater reliability is 0.99 (Podsiadlo & Richardson, 1991). Podsiadlo and Richardson (1991) tested validity by measuring the correlation between the TUG and the subjects’ balance ( $r=-.55$ ), gait speed ( $r=-.55$ ), and functional capacity ( $r=-.51$ ). The TUG score was the average of the two trials in minutes and seconds (see Table 8). This test took 5 minutes to complete.

*Aerobic fitness (submaximal exercise test).* Peak oxygen consumption ( $VO_{2peak}$ ) during performance of a graded exercise test is considered the “gold standard” measure of aerobic fitness (Vanhees et al., 2005).  $VO_2$  max is reached if the participant demonstrates a plateau in  $VO_2$  as the work rate continues to increase; however, usually less than 50% of the subjects tested demonstrate that plateau (Davis, 2006). Therefore, the participant is said to have reached  $VO_2$  peak. However, since conducting a  $VO_2$  max test in the laboratory is costly and time consuming, and would have limited the subject pool geographically, participants were tested in the field, using a submaximal test of aerobic performance.  $VO_2$  max was then estimated based on the results of the test. The Rockport One-Mile Fitness Walking Test has been used and shown to be valid and reliable in both fit and unfit populations across a wide age range and both genders (Kline et al., 1987) Therefore, aerobic fitness was determined with The Rockport One-Mile

Fitness Walking Test. Kline et al. (1987) tested 343 healthy subjects, ages 30 to 69 years, who each performed the 1-mile timed walk twice. Validity for heart rate ( $r=.93$ ) and time ( $r=.98$ ) were reported, as was reliability for heart rate ( $SEE=7.6$  bpm) and time ( $SEE = 0.26$  min).

Prior to the 1-mile walk, body weight, age and gender were recorded. Participants were asked to walk one mile (1,609 m) as fast as possible, without running or jogging. This test was conducted outside on a flat level surface or inside on a track. Each participant was secured with a Polar heart rate monitor and peak heart rate was recorded immediately after completion of the walk. The PI used a digital stop watch to measure the time of the walk to the nearest minute and hundredths of a minute. Participants continued to walk to cool down for up to 5 minutes. Participants were tested individually. Lastly, the PI was only allowed to give encouragement every 2 minutes or once every 400 meters (if on a track) by saying one or all of the following: “Good job. Keep up the good work. Almost there. Keep working hard.” This test took 12-25 minutes to complete.

$VO_2$  max in ml/kg/min was estimated, as presented in Table 8, using the inputs obtained (body weight (lbs), age (yr), gender (male = 1, female = 0), time for the walk in minutes and hundredths of a minute, and HR peak), as follows:  $VO_2$  max (ml/kg/min) =  $132.853 - (0.0769 \times \text{weight}) - (0.3877 \times \text{age}) + (6.315 \times \text{gender}) - (3.2649 \times \text{time}) - (0.1565 \times \text{HR peak})$  (Kline et al., 1987).

Table 8  
*Predictor Variable Scores Used in Statistical Analyses*

<b>Instrument</b>	<b>Description</b>	<b>Scores</b>
<i>The Aerobics Center Longitudinal Study Physical Activity Questionnaire (modified)</i>	Self-reported level of physical activity	Calculated METS Number of vigorous bouts of physical activity
<i>The Timed “Up and Go” Test</i>	Functional mobility	Average of 2 Timed Trials
<i>The Rockport One-Mile Fitness Walking Test</i>	Walked 1-mile as quickly as possible	Estimated VO <sub>2</sub> max from recorded time to completion, gender, body weight, age, and peak HR at end of walk

*Assessment of Dependent Variables*

*Mini mental state examination (MMSE).* The MMSE, an 11-question test, measured cognitive and mental status in adults by assessing orientation, registration, attention and calculation, recall, and language. It took 10 minutes to administer. The maximum score was 30 and a score of 24 or lower was considered indicative of cognitive impairment (Kurlowicz & Wallace, 1999). If greater than 5 subjects scored a 24 or lower on the MMSE, then they would be analyzed separately. This did not occur, as no subjects scored below a 26. This test took 5 minutes to complete. One score was calculated and used in the analyses.

*General demographic and health status questionnaire (GDHSQ).* This questionnaire assessed: doctor/patient and nutritionist/patient satisfaction, as measured with a 5-point Likert scale, demographics (age, gender, and education level), contact information, medications, diet adherence rate perception, CD diagnosis type, and age at diagnosis. This questionnaire took 10-20 minutes to complete. The questionnaire assessed the covariates of interest, and some additional demographic areas for descriptive reporting.

*Trail making test (A&B).* The primary task, Trail Making, is the most widely used task to assess divided attention and cognitive flexibility (Lezak et al., 2004). Further, Trail Making is responsive to detecting dementia and brain injury. The Trail Making Test is currently part of the Halstead Battery and it measures attention, speed and mental flexibility (Strauss, Sherman, & Spreen, 2006). The test has two parts, part A, which requires the participant to connect 25 encircled numbers in the correct order, and part B, which requires connecting 25 encircled numbers and letters in alternating order. Reliability coefficients have been reported between 0.46 and 0.79 for Part A and between 0.44 and 0.89 for Part B (Strauss et al., 2006). This test took 5 minutes to complete. Time in seconds that it took complete Part A and Part B were recorded. Next a ratio was calculated by dividing the Part B time in seconds by the Part A time in seconds. Finally, the difference score was calculated by subtracting Part A time in seconds from Part B time in seconds. Two scores (Trails A, Trails B), as presented in Table 9, were calculated.

*Digits backward (WIS-A, WMS).* Digits backward measures span of immediate verbal recall and is included in the Wechsler batteries' intelligence and memory scales. The list of digits is read to the participant and upon hearing the digits, the participant must repeat the digits back to the investigator in reverse order. There are seven pairs of randomly ordered digit sequences. The test measures auditory attention, short-term retention capacity, and working memory. The test is sensitive to left hemisphere damage, visual field defects, diffuse damage, and lesions (Lezak et al., 2004). This test took 5 minutes to complete. The score was the total number of correctly repeated digit lists. (see Table 9).

*Verbal Fluency.* The verbal fluency test consists of three, one-minute word naming trials and usually uses the letters, F-A-S. The following instructions were given: *"I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For example, if I say "b" you might give me "bad, battle, bed..." I do not want you to use words that are proper names such as "Boston, Bob, or Buick." Also, do not use the same word with different endings such as "eat" and "eating." Any questions? (pause). Begin when I say the letter. The first letter is F. Go ahead."* Slang words, foreign words, proper names, wrong words, nonwords and repetitions are not included in the total. A stop watch was used. Using letters F-A-S, internal reliability was reported to be  $r=.83$ . The letter "L" was used as an alternate. This test took 7 minutes to complete. Scoring for verbal fluency was the sum of the acceptable words produced during the trials.

*The clock drawing test.* The clock drawing test is able to detect dementia and executive function impairment. There are many different versions and administration systems of the Clock Drawing test. The version that was used in this study was the CLOX test developed by Royall, Cordes, and Polk (1998). The CLOX test has two parts, the CLOX1 and CLOX2. The CLOX1 detects executive function and uses the following directions: ‘Draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them.’ CLOX2 requires the subject to copy a clock that the investigator drew after the subject has observed it. Five minutes is required to complete the two clock drawing tasks. Two scores are obtained, CLOX1 and CLOX2. Reliability (internal consistency) in elderly subjects (45 years old and well and 45 years old and with probable Alzheimer’s Disease) was found to be  $r=.82$ , while between rater reliability was also high for both the CLOX1 ( $r=.84$ ) and CLOX2 ( $r=.93$ ) (Royall et al., 1998). The CLOX1 scores and the EXIT25 (executive test) and Mini Mental State Exam were highly correlated (partial  $r^2=.71$ ) after adjusting for age and education and the Mini Mental State Exam and CLOX2 were highly correlated (partial  $r^2=.74$ ) (Royall et al., 1998). CLOX 1 and CLOX 2 scores were calculated and used in the statistical analyses (see Table 9). This test took 3-5 minutes to complete.

Table 9  
*Executive Function Criterion Variable Scores Used in Statistical Analyses*

<b>Instrument</b>	<b>Description</b>	<b>Scores</b>
<i>Trail Making Test (A&amp;B)</i>	Measures attention, speed and mental flexibility.	Trails A score Trails B score
<i>Digits Backward</i>	Measures span of immediate verbal recall, auditory attention, short-term retention capacity, and working memory.	Total score
<i>Verbal Fluency</i>	Consists of three, one-minute word naming trials that use the letters, F-A-S. A sensitive indicator of brain dysfunction. Sensitive to frontal lobe damage.	Total score for 3 letters
<i>The CLOX Test</i>	Detects dementia and executive function impairment.	CLOX 1, CLOX 2 (copy task)

*Medical outcomes study (MOS) 36-item short-form health survey.* The 36-item Health Survey is part of the Medical Outcomes Study (MOS). A modified version, the MOS 36-item Short-form Health Survey (SF-36) (Ware & Sherbourne, 1992) was used to measure perceived level of functioning. The SF-36 measures eight health concepts and general health perceptions: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions (Hays, Sherbourne, & Mazel, 1993). The SF-36 contains eight subscales, one Reported Health Transition score, and two aggregate scores. The eight subscales, which are presented in Figure 2, are as follows: Physical Functioning (SF-36 PF), Role-Physical (SF-36 RP),

Bodily Pain (SF-36 BP), General Health (SF-36 GH), Vitality (SF-36 VT), Social Functioning (SF-36 SF), Role-Emotional (SF-36 RE), and Mental Health (SF-36 MH). The two aggregate scores are the SF-36 Physical Component Score (SF-36 PCS) and SF-36 Mental Component Score (SF-36 MCS) (see Table 10).

According to Lox et al. (2006), the SF-36 has been used to assess the effect of exercise on HRQL in the frail elderly (Schechtman & Ory, 2001), cardiac rehabilitation patients (Milani, Lavie, & Cassidy, 1996), women with breast cancer (Segal et al., 2001), and people with Type 2 diabetes (Kirk et al., 2001). This test took 10 minutes to complete. The SF-36 Physical Component Score and SF-36 Mental Component Score were used in the analyses.

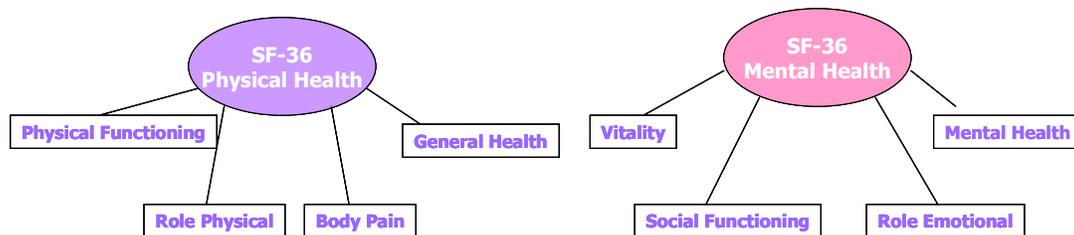


Figure 2. SF-36 diagram

*Celiac disease questionnaire (CDQ)*. This is a CD-specific measure of HRQL, which has four scales: GI symptoms, emotional well-being, social restrictions and disease-related worries. The CDQ has four scales, as presented in Figure 3, which are: Emotion, Social, Worries, and Gastrointestinal. It takes 10 to 20 minutes to complete. Each scale has seven items and the patient responds using a 7-point Likert scale. A high score is indicative of good HRQL. The CDQ was developed and validated by Häuser et

al. (2007). The internal consistency (Cronbach alpha) and retest reliability (Pearson correlation) for each of the subscales have been reported by Häuser et al. (2007). : emotion ( $\alpha=0.91$ ;  $r=0.52$ ), social ( $\alpha=0.81$ ;  $r=0.55$ ), worries ( $\alpha=0.81$ ;  $r=0.89$ ), gastrointestinal ( $\alpha=0.80$ ;  $r=0.45$ ), and total score ( $r=0.57$ ). This test took 10 minutes to complete. Four subscale scores, as well as a total score (CDQ total) were calculated, but the total score was used first during the statistical analyses (see Table 10).

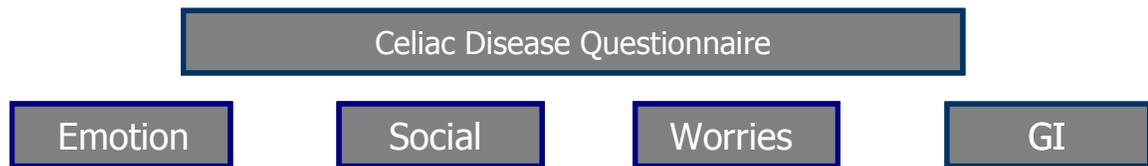


Figure 3. Celiac Disease Questionnaire diagram

Table 10  
*HRQL Criterion Variable Scores Used in Statistical Analyses*

<b>Instrument</b>	<b>Description</b>	<b>Scores</b>
<i>SF-36</i>	HRQL (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health)	Physical Component Score Mental Component Score
<i>Celiac Disease Questionnaire</i>	Celiac Disease specific HRQL (emotion, social, worries, gastrointestinal)	CDQ Total

### *Experimental Procedures*

The introductory letter outlined and introduced the research study and explained the volunteer parameters, consent, and confidentiality. It was emailed or U.S. mailed to the participants. This letter asked the participants to email or call if interested in participating in the study. The introductory letter also explained the inclusion and exclusion criteria as outlined below. Eligibility was assessed over the telephone by using the PARQ. Eligible participants were scheduled for testing. Upon arrival at the testing site, the PI introduced herself and explained the purpose of the study, including the surveys, physical activity testing, and the cognitive testing. The participant was then asked to read and sign an informed consent. All human studies were approved by the Institutional Review Board at the University and therefore have performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

The participant completed the MMSE. This took approximately 5 minutes. After reading the instructions, the participant completed and answered questions in the General Demographic and Health Status Questionnaire. This took about 10-20 minutes to complete. Following completion of that questionnaire, the participant completed the cognitive testing, which consisted of the Trail Making Test (A&B), Digits Backward verbal fluency, and the CLOX test. The cognitive testing took approximately 15-20 minutes. After the cognitive testing was completed, they were directed to complete the 36-Item Short Form Health Survey (SF-36), the Celiac Disease Questionnaire, and the Aerobics Center Longitudinal Study Physical Activity Questionnaire. The final three questionnaires took approximately 30-45 minutes to complete.

After the questionnaires were completed, participants completed the TUG, a measure of functional fitness, and the Rockport 1-Mile Fitness Walking Test, a submaximal test of aerobic fitness. These took approximately 5 minutes, and 12-25 minutes to complete, respectively. Debriefing about the study occurred after the Rockport 1-Mile Fitness Walking Test. See Figure 4 for a pictorial description of the experimental procedures.



*Figure 4.* Flow of procedures

## *Power Analyses*

### *Health-Related Quality of Life Variables*

To provide sufficient statistical power for the HRQL variables, data needed to be collected on a minimum of 15 subjects. This sample size was determined based upon a power of 80% and the data from the pilot study. The data from the pilot study were used to inform Table 11. There are columns for both four and eight prior covariates. The covariates that were included in the pilot study were gender, age (years), biopsy (yes/no), and gluten free diet adherence perception (% of the time). However, subject size for the current study was estimated using eight covariates since additional potentially relevant covariates have been identified since conducting the pilot study. The predictor variables used in the pilot study and used in the proposed study are VO<sub>2</sub> peak, and a principal components factor score to reflect physical activity (combined METs per week and number of vigorous bouts per week). These are identified as the “number of covariates to add, B” in the table. The dependent variables for the pilot study and for the proposed study are the SF-36 Physical Component Score (PCS) and the SF-36 Mental Component Score (MCS) and these represent the columns in Table 11. The RA<sup>2</sup> values of 0.338 and 0.568 and the “Increase in R<sup>2</sup>” values of 0.398 and 0.322 were taken from the pilot study and used as estimates of the predicted explained variance for the proposed study. Given this data, the predicted necessary sample size to insure sufficient statistical power is provided in the final row of the table. Therefore, 11-15 subjects were needed with a power of 80% to detect an increase in R<sup>2</sup> between .32 and .40 for HRQL.

Table 11

*Same Size Needed with 80% Power to Detect an Increase in R<sup>2</sup> between .32 and .40*

Power Analysis Variables	HRQL			
	PCS		MCS	
Number of prior covariates	4	8	4	8
Alpha	0.05	0.05	0.05	0.05
Correlation, RA <sup>2</sup> , for A covariates	0.338	0.338	0.568	0.568
Number of covariates to add, B	2	2	2	2
Increase in R <sup>2</sup> = RAB <sup>2</sup> - RA <sup>2</sup>	0.398	0.398	0.322	0.322
Power (%)	80	80	80	80
N	<b>13</b>	<b>15</b>	<b>11</b>	<b>14</b>

*Note.* PCS=SF-36 Physical Component Summary Score; MCS=SF-36 Mental Component Summary Score; N = number of subjects needed; RA<sup>2</sup> = correlation of covariates

### *Cognitive Performance Variables*

Although analyses using the cognitive variables were secondary, a power analysis was conducted to identify the range of subjects needed. No pilot data was available for the cognitive performance variables assessed; therefore, the number of subjects needed to insure sufficient statistical power (.80) to detect a range of possible relationships was identified. A range of potential increases in R<sup>2</sup> that might be detected was identified (vertical). A range of correlations (R<sup>2</sup>) for the covariates age and gender are also listed (horizontal). The number of subjects needed is listed in Table 12. Approximately 38-78 subjects were needed to have enough power to detect an effect (.08 to .10) of aerobic fitness on cognitive performance given a prior correlation of the covariates (.338 to .568). The prior correlation of the covariates was derived from pilot data (study is mentioned above) on a Celiac Disease sample that assessed HRQL. The effect of aerobic fitness on cognitive performance is 0.08-0.10 and this is based on data obtained from Etnier et al.'s (2006) meta-analysis which showed that  $r=.29$ ;  $r^2 = .0841$ . Thus, given a sample size

between 38 and 78, the analyses would have sufficient statistical power to detect an effect size of .08-.10 given that covariates account for 30-55% of the variance. Given that this was a secondary analysis and that the effects when both aerobic fitness and physical activity are accounted for could be expected to be slightly larger, a sample size of 40 subjects is proposed (situations for which this will result in sufficient statistical power are identified in blue font).

Table 12  
*Number of Subjects (N) Needed Based on the Explained Variance Due to Covariates and Possible Increases in Explained Variance as a Function of the Current Predictors (Physical Activity and Aerobic Fitness)*

Increase in RA <sup>2</sup>	RA <sup>2</sup>									
	.10	.15	.20	.25	.30	.35	.40	.45	.50	.55
.05	167	158	148	139	129	119	110	100	90	81
.08	102	96	90	84	78	72	66	60	54	48
.10	81	76	71	66	62	57	52	47	43	38
.12	66	62	58	54	50	46	43	39	35	31
.14	56	53	49	46	43	39	36	32	29	26
.16	48	46	43	40	37	34	31	28	25	22
.18	43	40	37	35	32	29	27	24	22	19
.20	38	35	33	31	28	26	24	22	19	17

*Note.* Power = 80%; Alpha = 0.05; Number of prior covariates is four; Number of covariates to add is two; RA<sup>2</sup> = correlation of covariates

### *Statistical Analyses*

Scores for physical activity, aerobic fitness, TUG, HRQL, and Executive Function were compared to normative values and/or mean values from similar populations. All statistical analyses were conducted using SPSS 14.0 (SPSS Incorporated, Chicago, IL).

#### *Covariates*

Seven of the eight (age, gender, diet adherence rate perception, diagnosis type, age at diagnosis, general cognition, and degree of satisfaction with information provided by doctor at diagnosis) hypothesized potential covariates were considered for inclusion in the analyses when the predictor variables (MET hours per week, number of bouts of vigorous physical activity, estimated VO<sub>2</sub> max) were significant. Bivariate correlations were used to determine if they would be included.

Satisfaction with information provided by current GI doctor was not available for inclusion, since only 27 of the 47 subjects were actually seeing a GI doctor for CD. Covariates that were categorical (and that were not binary) were dummy coded. The covariate “diagnosis type” was collapsed from 4 types to 2 types (0=any type of biopsy, 1=blood test or other).

Bivariate correlations were conducted with the seven covariates and each of the dependent variables. If a Pearson correlation was significant ( $p < .05$ ), then that covariate was considered for inclusion. The covariates were included in both a canonical correlation model and a multivariate multiple regression as predictors, and the canonical correlation (from the canonical correlation model) and p values (from the multivariate multiple regression) were judged to determine if the covariate would stay in the model or

be removed. Covariates were examined individually and if a particular covariate did not contribute to the model, based on a high p value, it was removed and the analysis was repeated. However, if removal of the covariate resulted in a large decrease in the canonical correlation, then the covariate was added back into the model.

### *Analyses of Aims*

Exploratory bivariate correlations were conducted for the HRQL variables and the executive function variables with physical activity, aerobic fitness, and TUG.

Canonical correlations were used for all dependent variables (See Table 13).

Canonical correlation is a subclass of multivariate regression (Green, Halbert, & Robinson, 1966). This method is used when a researcher is interested in relationships between sets of variables (Green et al., 1966; Levine, 1977). The canonical correlation allows for a relationship to be established between two canonical or latent variables. These variables represent a set of independent variables and a set of dependent variables. Linear combinations of the two sets of latent variables are created and these will have maximum correlation with one another (see Figure 5). As a result, a canonical correlation, represented by  $R_c$ , is derived. The  $R_c$  is interpreted the same as a Pearson's  $r$ . Standardized coefficients (or standardized canonical weights) for each variable are also provided. These weights are sometimes useful in determining the relative importance of each variable in the relationship by looking at the sign and magnitude of the standardized weight (Alpert & Peterson, 1972). However, this procedure is to be taken with caution in that it is difficult to determine the relative importance for a couple of reasons. For example, a small weight could mean one of two things: that the variable is unimportant in

the relationship, or that the variable is so highly correlated with another variable that its weight has been reduced. Second, interpretation is difficult because all of the variable are correlated with one another simultaneously (Alpert & Peterson, 1972). That is, an individual variable's importance is hard to determine given that the canonical correlation is derived from the optimal linear combination of those variables, while accounting for the inner correlation among those variables. Therefore, removing or adding any variables to the set changes the dynamics of the relationship. Therefore, due to the complex nature of these interpretations, the importance of the standardized canonical weights associated with each individual variable was not identified.

Table 13  
*Aims and Components of Canonical Composites*

<b>Aim</b>	<b>Predictors</b>	<b>Criterion</b>	<b>Components of the Criterion</b>
#1 (Primary)	PA and AF	HRQL	SF-36 PCS, SF-36 MCS Celiac Disease Questionnaire Total
#2 (Secondary)	PA and AF	Executive Function	Trail Making A, Trail Making B, Digit Span, Verbal Fluency, CIOX 1, CIOX 2
Exploratory	Functional Fitness	HRQL & Executive Function	Same as #1 and #2 above

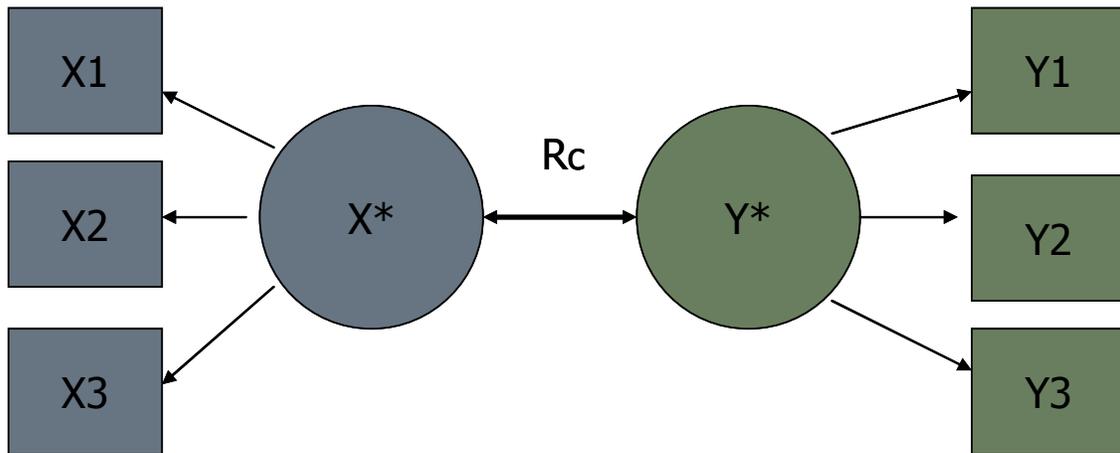


Figure 5. Canonical correlation

A canonical composite of the total HRQL scores (CDQ total, SF-36 PCS, and SF-36 MCS) was correlated separately with MET hours per week, number of vigorous bouts of physical activity per week, estimated VO<sub>2</sub> max, and TUG. See Figure 6 for an example of the canonical correlation for the HRQL composite with vigorous bouts of physical activity per week.

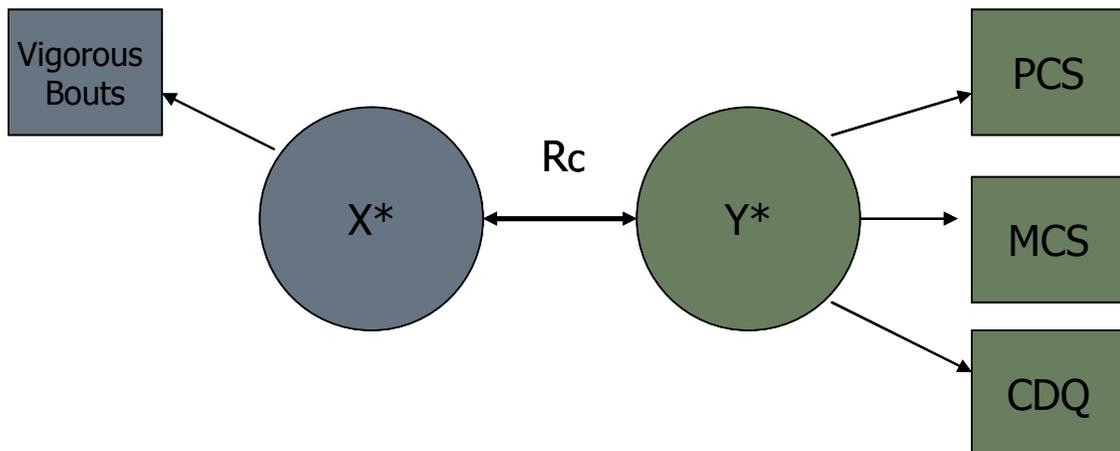


Figure 6. Canonical correlation for HRQL with Vigorous Bouts

Canonical correlations were used for all executive function dependent variables (Trails A, Trails B, Digits Backwards, Verbal Fluency, CLOX 1, CLOX 2). Executive function was correlated separately with MET hours per week, number of vigorous bouts of physical activity per week, estimated VO<sub>2</sub> max and TUG. See Figure 7 for an example of the canonical correlation for the executive function composite with vigorous bouts of physical activity per week.

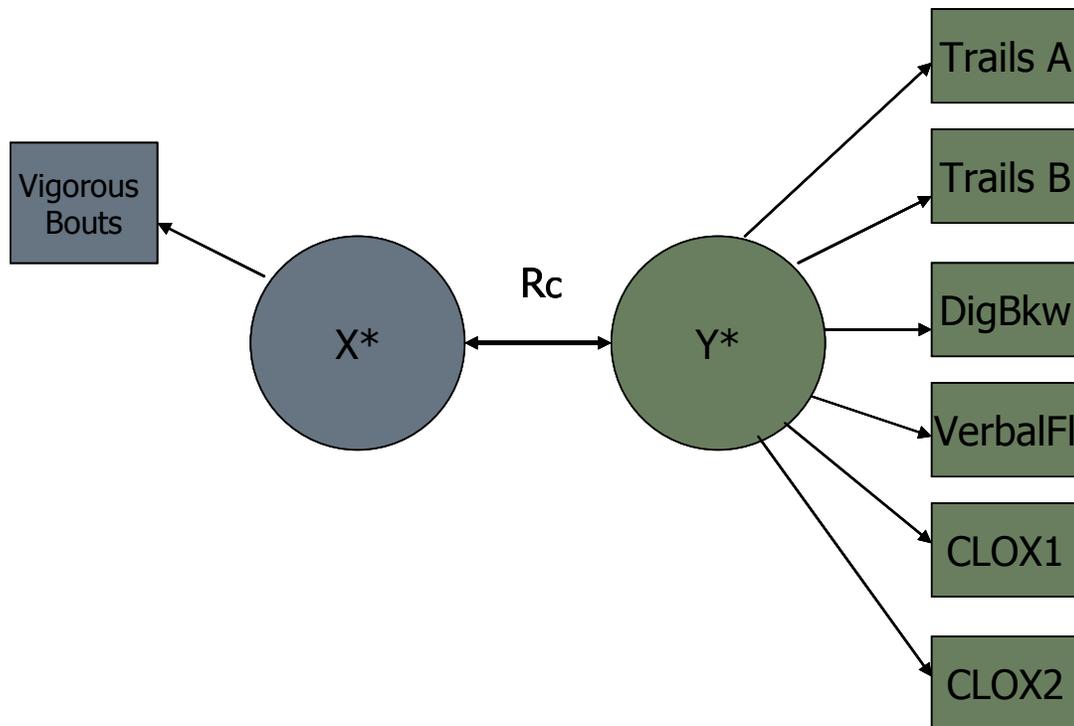


Figure 7. Canonical correlation for Executive Function with Vigorous Bouts

## CHAPTER V

### RESULTS

#### *Descriptive Information and Statistics*

Descriptive information for this CD sample is presented in Table 14. Means and standard deviations for all variables are presented in Table 15. Descriptive information for questions that assessed doctor and nutritionist satisfaction are presented in Table 16.

Table 14  
*Descriptive Statistics for the CD Sample*

<b>Participation</b>	<b>N</b>
N	47
Female (n)	34
Percent (%) Female	72.34%
Mean Score on Mini Mental State Exam (MMSE) (SD)	29 (4)
Diagnosis Type	
Biopsy / Endoscopy of Small Intestine (n)	37
Dermatitis Herpetiformis (n)	1
Capsule Endoscopy (n)	1
Blood Test (n)	7
Other (n)	1
Yes to GF Diet Adherence Within Past 2-weeks (n)	47
100% Adherence (n)	43
90% Adherence (n)	4

<b>Measure of Variable</b>	<b>Mean (SD)</b>
Mean (SD) Age	49 (12.54)
Mean (SD) Age (months) at Diagnosis	507.3 (163.83)
Mean (SD) Time (months) Since Diagnosis to Research Study	89.79 (99.69)
Mean (SD) Time (months) Adhering to the GF Diet	87.3 (100.27)
Mean (SD) Bouts of Physical Activity / Week	3.36 (2.75)
Mean (SD) MET Hours / Week	61.15 (40.39)
Mean (SD) VO <sub>2</sub> max (ml/kg/min)	34.20 (8.0)
Mean (SD) VO <sub>2</sub> max (ml/kg/min) - Males	40.45 (5.91)
Mean (SD) VO <sub>2</sub> max (ml/kg/min) - Females	31.82 (7.44)
Mean (SD) TUG (minutes)	4.71 (.94)

Table 15

*Descriptive Statistics for Physical Activity, Aerobic Fitness, Functional Fitness, HRQL, and Executive Function Variables (N=47)*

<b>Variable</b>	<b>Mean</b>	<b>SD</b>
Number of Vigorous Bouts of PA/week	3.36	2.75
Number of MET hours/week	61.15	40.39
Estimated VO2 max (ml/kg/min)	34.20	8.00
Timed Up and Go test <sup>a</sup> (seconds)	4.71	.94
CDQ – Emotion	37.19	5.49
CDQ – Social	45.06	4.16
CDQ – Worries	41.74	6.04
CDQ – Gastrointestinal	41.38	5.36
CDQ – Total Score	165.38	15.72
SF-36 Physical Functioning	53.99	4.23
SF-36 Role Personal	52.63	6.39
SF-36 Bodily Pain	49.44	6.11
SF-36 General Health	50.36	9.17
SF-36 Vitality	52.69	8.22
SF-36 Social Functioning	53.02	6.17
SF-36 Role Emotion	52.90	5.20
SF-36 Mental Health	53.42	6.16
SF-36 Physical Component Score	51.27	5.49
SF-36 Mental Component Score	53.17	5.66
Trails A <sup>a</sup> (seconds)	25.48	9.35
Trails B <sup>a</sup> (seconds)	55.79	20.20
Trails B / Trails A ratio score	2.28	0.63
Trails B – Trails A difference score	30.31	14.41
Digits Backwards	7.81	2.22
Verbal Fluency	43.26	10.83
CLOX 1	13.47	0.99
CLOX 2	14.64	0.64

*Note.* <sup>a</sup> lower score indicates better performance

Table 16  
*Information about Doctor/Nutritionist Consultations and Satisfaction with Doctors/Nutritionist (N=47)*

Variables	n
Satisfaction with information provided by doctor at diagnosis	
<i>Not at all (1)</i>	6
<i>Slightly (2)</i>	9
<i>Moderately (3)</i>	12
<i>Quite a bit (4)</i>	11
<i>Extremely (5)</i>	9
Number of CD patients currently seeing a GI doctor for CD	27
Satisfaction with information provided by current GI doctor	
<i>Not at all (1)</i>	1
<i>Slightly (2)</i>	6
<i>Moderately (3)</i>	4
<i>Quite a bit (4)</i>	6
<i>Extremely (5)</i>	10
Number of CD patients who were referred to a nutritionist at diagnosis	26
Number that attended a consultation with a nutritionist at diagnosis, if referred	19
Satisfaction with information provided by the nutritionist at diagnosis, if referred and if attended consultation	
<i>Not at all (1)</i>	4
<i>Slightly (2)</i>	5
<i>Moderately (3)</i>	3
<i>Quite a bit (4)</i>	7
<i>Extremely (5)</i>	1

*Celiac Disease sample compared to normative values for dependent variable measures*

The CD sample had a mean age of 49 years; therefore, their scores for SF-36 PCS and SF-36 MCS were compared to the norms for the U.S. population, males and females, ages 45-54 (N=1561) (Ware, Kosinski, & Dewey, 2000). The CD sample scored higher, indicating better quality of life, than the normative sample on both SF-36 PCS and SF-36 MCS. The scores obtained from the CD sample for the CDQ were compared to subjects

( $N=1000$ ), also with CD, who were used to validate the CDQ questionnaire (Hauser et al., 2007). Our CD sample scored higher on all 4 subscales of the CDQ and the total CDQ than the normative group. See Table 17 for a comparison of the CD sample to normative values for the SF-36 and CDQ.

Table 17  
*CD Sample Compared for Normative Values for the SF-36 and CDQ*

<b>HRQL Variables</b>	<b>Dissertation Sample</b>	<b>Normative Sample</b>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>
SF-36 PCS	51.27 (5.49)	49.46 (10.22)
SF-36 MCS	53.17 (5.66)	49.92 (10.22)
CDQ Total	165.38 (15.72)	151.1 (25.2)

The CD sample also has scores that were similar to normative values for the MMSE group with similar ages and years of education (see Table, 18). When compared to the verbal fluency normative group with the same level of education, the CD sample performed slightly better (see Table 19).

Table 18  
*CD Sample Compared for Normative Values for the MMSE*

Variable	Dissertation Sample		Normative Sample 1*		Normative Sample 2**		Normative Sample 3***	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MMSE	29	4	29	1.6	28	1.9	26	2.5

*Note.* \*45-49 year olds with college experience normative group; \*\*45-49 year olds with a high school diploma; \*\*\*45-49 year olds with five to eight years of education; Crum, Anthony, Bassett and Folstein (1993)

Table 19  
*CD Sample Compared for Normative Values for Verbal Fluency*

Executive Function Variable	Dissertation Sample	Normative Group 1*	Normative Group 2**
	Mean (SD)	Mean (SD)	Mean (SD)
Verbal Fluency	43.26 (10.83)	40.5 (10.7)	44.7 (11.2)

*Note.* \*the normative group (N=268), with 9-12 years of education \* the normative group (N=242) with 13-20 years of education Tombaugh, Kozak, and Rees (1999)

The CD sample was considered to be in the 75<sup>th</sup> percentile when compared to normative values, in the 45-54 age group, for Trails Making A and Trails Making B (Tombaugh, 2004). A higher score is indicative of worse performance.

On the Digit Span Backwards tests, the CD sample performed better than a mixed clinical sample (N=44) (see Table 20). The CD sample scored better than both the young adult controls (N=62) and independent living retirees (N=45) on both the CLOX1 and CLOX2 (Royall et al., 1998).

Table 20  
*CD Sample Compared for Normative Values for Digit Span Backwards*

	<b>Dissertation Sample</b>	<b>Normative Sample*</b>
<b>Executive Function Variable</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
Digit Span Backwards	7.81 (2.22)	6.02 (1.73)

*Note.* \*Data from Wilde and Strauss (2002)

*Celiac Disease sample compared to normative values for independent variable measures.*

This CD sample completed more vigorous bouts of physical activity/week and participated in more MET hours of physical activity per week than the normative comparison groups (see Table 21).

Table 21

*CD Dissertation Sample's Physical Activity Levels and Participation Compared to ACSM Physical Activity Recommendations*

<b>Physical Activity Measure</b>	<b>Dissertation Sample</b>		<b>Physical Activity Recommendation (ACSM)</b>	
	<b>Mean (SD)</b>	<b>% who meet Recommendation</b>	<b># Minutes/METs</b>	<b>% who meet Recommendation</b>
Vigorous bouts of physical activity/week	3.36 (2.75)	59.6%	20 minutes on 3 days/week*	48.8%**
MET hours/week	61.15 (40.39)	100%	7.5 to 12.5 MET hours/week*	48.8%**

*Note.* \*Haskell et al. (2007); \*\*CDC U.S. Physical Activity Statistics 2007, Centers of Disease Control and Prevention (2007) <http://apps.nccd.cdc.gov/PASurveillance/StateSumResultV.asp>

When compared to normative data on aerobic fitness, this CD sample of men and women was higher than the mean VO<sub>2</sub> max found for both men and women in the moderate fitness category ( $N=3837$  men;  $N=1110$  women) in the Aerobics Center Longitudinal Study (Stofan, DiPietro, Davis, Kohl, & Blair, 1998) (see Table 22).

Table 22

*CD Dissertation Sample's VO<sub>2</sub> max compared to moderate fitness category in the Aerobics Center Longitudinal Study*

	<b>Dissertation Sample</b>	<b>Normative Group*</b>
<b>Aerobic Fitness Variable</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
VO <sub>2</sub> max - Men	40.45 (5.91)	37.6 (3.8)
VO <sub>2</sub> max - Women	31.82 (3.8)	29.3 (3.6)

*Note.* \*Aerobics Center Longitudinal Study (Stofan, DiPietro, Davis, Kohl, & Blair, 1998)

Finally, the CD sample's score ( $M=4.71$ ,  $SD=.94$ ) on the TUG test was lower (faster score) than the score obtained from ten normal controls with a mean age of 75 years ( $M=8.5$ ) and 60 elderly patients with a mean age of 79.5 years (time ranged 10 to 240 seconds) (Podsiadlo & Richardson, 1991). Since the TUG is used mainly in elderly patients, we were unable to find normative values for younger to mid-age adults.

#### *Bivariate Correlations Among the Predictor Variables*

Bivariate correlations showed that vigorous bouts of physical activity/week was significantly moderately correlated with MET hours/week ( $r = .46$ ;  $p=0.001$ ). None of the other relationships between MET hours/week, VO<sub>2</sub> max, or physical activity/week were statistically significant.

Bivariate correlations showed that the TUG was positively correlated with estimated VO<sub>2</sub> max ( $r = -.59$ ;  $p<0.001$ ) and number of vigorous bouts of physical activity/week ( $r = -.33$ ;  $p=0.02$ ), such that as TUG decreased, physical function improved (i.e. shorter time to complete the task), and estimated VO<sub>2</sub> max and number of vigorous

bouts of physical activity/week increased. TUG was not correlated with MET hours/week ( $r < .04$ ).

*Bivariate correlations between the predictor and criterion variables*

Bivariate correlations were conducted for the SF-36 and CDQ with measures of physical activity, aerobic fitness, and functional fitness (see Table 23, Table 24, and Table 25). Bivariate correlations were conducted for the SF-36 with the CDQ (see Table 26 and Table 27). Bivariate correlations were conducted for the executive function variables (Trails A, Trails B, Digits Backwards, Verbal Fluency, CLOX 1, and CLOX 2) with the same predictor variables (See Table 28)

A Bonferroni correction was used for the analysis between predictor variables and the HRQL variables. Sixty correlations were conducted, and thus the p value for significance was set at  $p = .001$ . A Bonferroni correction was use for the analysis between the predictor variables and the executive function variables. Twenty-four correlations were conducted, and thus the p value for significant was set at  $p=.002$ . There were no significant relationships between the predictor variables and criterion (either HRQL or executive function) after making the Bonferroni corrections.

Table 23

*Correlations for SF-36 Physical subscales and SF-36 PCS aggregate score with Predictor Variables*

<b>Measure</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>
1. Vig Bouts	--							
2. Met Hours	.46**	--						
3. VO <sub>2</sub> max	.19	-.12	--					
4. TUG <sup>a</sup>	-.33*	.04	-.59**	--				
5. SF-36 PF	.21	.03	.44**	-.37*	--			
6. SF-36 RP	.02	-.11	.17	-.14	.41**	--		
7. SF-36 BP	.17	-.01	.14	.03	.36*	.45**	--	
8. SF-36 GH	.23	.07	-.08	-.02	.62**	.51**	.38**	--
9. SF-36 PCS	.23	-.03	.22	-.21	.71**	.75**	.70**	.77**

*Note.* \*\* significant before a Bonferroni correction at  $p < .01$ ; \* significant before a Bonferroni correction at  $p < .05$ ; <sup>a</sup> lower score indicates quicker performance

Table 24

*Correlations for SF-36 Mental subscales and SF-36 MCS aggregate score with Predictor Variables*

<b>Measure</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>
1. Vig Bouts	--							
2. Met Hours	.46**	--						
3. VO <sub>2</sub> max	.19	-.12	--					
4. TUG <sup>a</sup>	-.33*	.036	-.59**	--				
5. SF-36 VT	.13	.15	-.06	-.13	--			
6. SF-36 SF	.03	-.05	.11	-.07	.21	--		
7. SF-36 RE	-.02	.02	.13	-.00	.27	.39**	--	
8. SF-36 MH	.05	.09	-.08	.13	.56**	.30*	.64**	--
9. SF-36 MCS	.01	.10	-.09	.08	.65**	.52**	.77**	.89**

*Note.* \*\* significant before a Bonferroni correction at  $p < .01$ ; \* significant before a Bonferroni correction at  $p < .05$ ; <sup>a</sup> lower score indicates quicker performance

Table 25  
*Correlations for Celiac Disease Questionnaire (CDQ) with the Predictor Variables*

Measure	1	2	3	4	5	6	7	8
1. Vig Bouts	--							
2. Met Hours	.46**	--						
3. VO <sub>2</sub> max	.19	-.12	--					
4. TUG <sup>a</sup>	-.33*	.04	-.60**	--				
5. CDQ Emotion	.06	.09	-.00	.03	--			
6. CDQ Social	.12	.24	-.06	.12	.35*	--		
7. CDQ Worries	.05	-.01	.07	-.12	.42**	.38**	--	
8. CDQ GI	.01	-.05	-.10	.13	.34*	.51**	.44**	--
9. CDQ Total	.08	.08	-.02	.04	.72**	.71**	.78**	.77**

Note. \*\* significant before a Bonferroni correction at  $p < .01$ ; \* significant before a Bonferroni correction at  $p < .05$ ; <sup>a</sup> lower score indicates quicker performance

Table 26  
*Correlations for the SF-36 Physical Subscales and SF-36 PCS Aggregate Score with the CDQ*

Measure	1	2	3	4	5	6	7	8	9
1. CDQ Emotion	--								
2. CDQ Social	.35*	--							
3. CDQ Worries	.42**	.38*	--						
4. CDQ GI	.34*	.51**	.44**	--					
5. CDQ Total	.72**	.71**	.78**	.77**	--				
6. SF-36 PF	.37*	.18	.61**	.14	.46**	--			
7. SF-36 RP	.54**	.16	.25	.03	.34*	.41**	--		
8. SF-36 BP	.32*	.44**	.32*	.37*	.48**	.36*	.45**	--	
9. SF-36 GH	.49**	.39**	.52**	.36*	.60**	.62**	.51**	.38**	--
10. SF-36 PCS	.37*	.28	.45**	.20	.45**	.71**	.75**	.70**	.77**

Note. \*\* significant before a Bonferroni correction at  $p < .01$ ; \* significant before a Bonferroni correction at  $p < .05$

Table 27

*Correlations for the SF-36 Mental Subscales and MCS Aggregate Score with the CDQ*

Measure	1	2	3	4	5	6	7	8	9
1. CDQ Emotion	--								
2. CDQ Social	.35*	--							
3. CDQ Worries	.42**	.38*	--						
4. CDQ GI	.34*	.51**	.44**	--					
5. CDQ Total	.72**	.71**	.78**	.77**	--				
6. SF-36 VT	.64**	.33*	.43**	.25	.56**	--			
7. SF-36 SF	.23	.30*	.10	.13	.24	.21	--		
8. SF-36 RE	.69**	.30*	.35*	.36*	.56**	.27	.39**	--	
9. SF-36 MH	.79**	.48**	.54**	.34*	.73**	.59**	.30*	.64**	--
10. SF-36 MCS	.78**	.46**	.41**	.37	.68**	.65**	.52**	.77**	.89**

*Note.* \*\* significant before a Bonferroni correction at  $p < .01$ ; \* significant before a Bonferroni correction at  $p < .05$

Table 28

*Correlations for Executive Function with the Predictor Variables*

Measure	1	2	3	4	5	6	7	8	9
1. Vig Bouts	--								
2. Met Hours	.46**	--							
3. VO <sub>2</sub> max	.85	-.12	--						
4. TUG <sup>a</sup>	-.33*	.04	-.59**	--					
5. Trails A <sup>a</sup>	-.06	.04	-.29*	.50**	--				
6. Trails B <sup>a</sup>	-.04	.13	-.25	.39*	.76**	--			
7. Digits	-.27	-.09	.23	-.25	-.42**	-.38*	--		
8. Verbal	-.28	-.26	.03	-.23	-.33*	-.34	.38**	--	
9. CLOX 1	-.34*	-.01	-.06	.22	-.01	-.24	.08	.13	--
10. CLOX 2	-.31*	-.11	.09	-.00	-.12	-.27	.15	.10	.47*

*Note.* \*\* significant before a Bonferroni correction at  $p < .01$ ; \* significant before a Bonferroni correction at  $p < .05$ ; <sup>a</sup> lower score indicates quicker performance

### *Specific Aim #1*

The canonical correlation ( $R_c=.23$ ) for the HRQL composite (CDQ total score, SF-36 PCS, and SF-36 MCS) with vigorous bouts of physical activity/week was not statistically significant. When MET hours / week was assessed with the HRQL

composite, the canonical correlation ( $R_c=.12$ ) was also not statistically significant.

Finally, the canonical correlation ( $R_c=.27$ ) for the HRQL composite with estimated VO<sub>2</sub> max was also not statistically significant. See Table 29 for a summary of the results. The standardized canonical coefficients for the HRQL composite are in Table 30. Due to non-significant findings for the HRQL variables, the covariates were not assessed.

Table 29  
*Specific Aim #1 (HRQL Composite) Results*

<b>Predictor</b>	<b>Correlation</b>	<b>Significant</b>
Vigorous bouts of physical activity/week	$R_c=.23$	no
MET hours/week	$R_c=.12$	no
VO <sub>2</sub> max	$R_c=.27$	no

Table 30  
*Standardized Canonical Coefficients for the HRQL Composite Variables*

<b>HRQL Composite Variables</b>	<b>Predictor Variable</b>			
	<b>Vigorous bouts/week</b>	<b>MET hours/week</b>	<b>Estimated VO<sub>2</sub> max</b>	<b>Timed Up and Go</b>
CDQ Total	.009	.458	.291	.472
PCS	-1.026	-.599	-1.031	-1.065
MCS	.179	.661	.373	.225
$R_c$	.23	.12	.27	.23

*Specific Aim #2*

The canonical correlation ( $R_c=.55$ ) for the executive function composite (Trails A, Trails B, Digits Backwards, Verbal Fluency, CLOX 1, CLOX 2) with vigorous bouts of physical activity/week was statistically significant ( $p=0.02$ ). The canonical correlations for the executive function composite with MET hours/week ( $R_c=.32$ ) and estimated VO<sub>2</sub> max ( $R_c = .36$ ) were not statistically significant. See Table 31 for a summary of the results. The standardized canonical coefficients for the executive function composite are in Table 32.

Table 31  
*Specific Aim #2 (Executive Function Composite) Results*

<b>Predictor</b>	<b>Correlation</b>	<b>Significant</b>
Vigorous bouts of physical activity/week	$R_c=.55$	$p=0.02$
MET hours/week	$R_c=.32$	no
VO2 max	$R=.36$	no

Table 32

*Standardized Canonical Coefficients for the Executive Function Composite Variables*

Executive Function Composite Variables	Predictor Variable			
	Vigorous bouts/week	MET hours/week	Estimated VO <sub>2</sub> max	Timed Up and Go
Trails A	-.094	.702	-.490	-.621
Trails B	-.538	-.664	-.293	-.237
Digits Backwards	-.459	-.039	.445	.051
Verbal Fluency	-.448	.866	-.323	.158
CLOX 1	-.480	-.413	-.370	-.527
CLOX 2	-.375	.352	.259	.093
$R_c$	.55*	.32	.36	.57*

*Note.* \* significant canonical correlation ( $R_c$ ) at  $p < .05$

Since vigorous bouts were a significant predictor of the executive function composite, covariates were assessed. Age and diagnosis age were significantly correlated with Trails A and Trails B (see Table 33 and Table 34). Vigorous bouts of physical activity/week was still a significant ( $p=0.024$ ) predictor ( $R_c=.65$ ,  $p=0.004$ ) of the executive function composite, when the covariates (age and diagnosis age) and vigorous bouts of physical activity/week were included in both the canonical correlation and multivariate multiple regression models; however, neither age nor diagnosis age were significant covariates. This was due to a high correlation ( $r= .80$ ,  $p=.000$ ) between age and diagnosis age. Therefore, diagnosis age was dropped from the model; age and vigorous bouts remained. Age was found to be a significant ( $p=0.004$ ) predictor ( $R_c=.625$ ,  $p=0.001$ ) of the executive function composite

Table 33

*Bivariate Correlation of the Potential Covariates (Age, Gender, GF Diet Adherence Perception, and Diagnosis Type) with the Executive Function Variables*

Measure	1	2	3	4	5	6	7	8	9
1. Trails A <sup>a</sup>	__								
2. Trails B <sup>a</sup>	.76**	__							
3 Digits	-.42**	-.38**	__						
4. Verbal	-.33*	-.34*	.38**	__					
5. CLOX 1	-.01	-.24	.08	.13	__				
6. CLOX 2	-.12	-.27	.15	.10	.47**	__			
7. Age	.42**	.43**	-.27	.17	-.04	-.19	__		
8. Gender	.04	.07	-.12	.07	.02	-.10	-.07	__	
9. GF Diet	-.10	.03	-.25	-.17	.24	.05	-.15	-.02	__
10. Diagnosis	-.11	-.12	-.04	.02	-.11	.08	-.18	-.15	.27

*Note.* \*\* significant before a Bonferroni correction at  $p < .01$ ; \* significant before a Bonferroni correction at  $p < .05$ ; a next to a lower score indicates quicker performance; GF Diet = Gluten Free Diet Adherence Perception; Diagnosis = Diagnosis Type

Table 34

*Bivariate Correlation of the Potential Covariates (Age at Diagnosis, MMSE, and Satisfaction with Information Provided by Diagnosis Doctor) with the Executive Function Variables*

Measure	1	2	3	4	5	6	7	8	9	10	11
1 Trails A <sup>a</sup>	__										
2 Trails B <sup>a</sup>	.76**	__									
3 Digits	-.42**	-.38**	__								
4. Verbal	-.33*	-.34*	.38**	__							
5. CLOX 1	-.01	-.24	.08	.13	__						
6. CLOX 2	-.12	-.27	.15	.10	.47**	__					
7. DiagAge	.34*	.34*	-.15	.26	.04	-.19	__				
8. MMSE	-.20	-.09	-.03	.22	.00	-.02	-.21	__			
9. DDS-1	.02	.17	.38**	.16	-.23	-.08	.06	.19	__		
10. DDS-2	.07	-.04	-.12	.08	-.06	-.10	.20	-.18	-.17	__	
11. DDS-3	-.16	-.13	-.02	-.15	-.05	.26	-.49**	.11	-.22	-.27	__
12. DDS-4	-.22	-.21	-.04	.10	.25	-.08	.14	.06	-.21	-.25	-.32*

*Note.* \*\* significant before a Bonferroni correction at  $p < .01$ ; \* significant before a Bonferroni correction at  $p < .05$ ; a next to a lower score indicates quicker performance; DiagAge= Age at Diagnosis; DDS = Satisfaction with Information Provided by Diagnosis Doctor (dummy variables 1, 2, 3, and 4)

### *Exploratory Aim*

The canonical correlation ( $R_c=.23$ ) for the HRQL composite (CDQ total score, SF-36 PCS, and SF-36 MCS) with TUG was not statistically significant (see Table 35).

The standardized canonical coefficients for the HRQL composite are in Table 30.

Covariates were not assessed due to non-significant findings.

The canonical correlation ( $R_c=.57$ ) for the executive function composite (Trails A, Trails B, Digits Backwards, Verbal Fluency, CLOX 1 CLOX 2) with TUG was statistically significant ( $p=0.01$ ) (see Table 35). The standardized canonical coefficients for the executive function composite are in Table 32.

Table 35  
*Exploratory Aim (HRQL Composite) Results*

<b>Predictor</b>	<b>HRQL</b>		<b>Executive Function</b>	
	<b>Correlation</b>	<b>Significant</b>	<b>Correlation</b>	<b>Significant</b>
Timed Up and Go (TUG)	$R_c=.23$	No	$R_c=.57$	$p=0.01$

Since TUG was a significant predictor of the executive function composite, the covariates were assessed. Age and diagnosis age were available for inclusion in the model since they were found to be significant with Trails A and Trails B (see Table 33 and Table 34). TUG remained a significant ( $p=0.012$ ) predictor ( $R_c=.64$ ,  $p=0.002$ ) of the executive function composite, when the covariates (age and diagnosis age) and TUG

were included in the both the canonical correlation and multivariate multiple regression models; however, neither age or and diagnosis age were significant covariates. This was due to a high correlation ( $r = .80, p = .000$ ) between age and diagnosis age. Therefore, diagnosis age was dropped from the model; age and TUG remained. Age was found to be a significant ( $p = .003$ ) predictor ( $R_c = .62, p = 0.00$ ) of the executive function composite,

## CHAPTER VI

### DISCUSSION

The first aim of this study was to identify the degree to which self-reported physical activity (MET hours per week; number of bouts of vigorous physical activity) and aerobic fitness predicted both HRQL (primary) and executive function (secondary) in CD patients, while the second aim was to explore the relationships between functional fitness and the same dependent variables. Forty-seven CD patients completed self-report questionnaires, cognitive tests, a functional fitness test, and a submaximal 1-mile walk test. Canonical correlations were used to assess the relationships between the physical activity, aerobic fitness, and functional fitness variables with HRQL and executive function. It was hypothesized that higher levels of physical activity, aerobic fitness, and functional fitness would be positively predictive of HRQL and executive function.

#### *Health Related Quality of Life*

The canonical correlations for HRQL with vigorous bouts of physical activity/week, MET hours/week, aerobic fitness and functional fitness were not significant. The non-significant results for vigorous bouts of physical activity/week were surprising since we had based our hypothesis on both the results of previous literature in chronic disease populations and the results of a recent pilot study which used similar measures to assess vigorous bouts and HRQL. Physical activity was assessed in both the pilot study and the current study by measuring MET hours/week and number of vigorous

bouts of physical activity/week. Further, this current study assessed HRQL with both the SF-36 and the CDQ; the pilot only assessed HRQL with the SF-36. When physical activity is measured, vigorous bouts is usually the most reliable predictor, given that participants are more able to accurately recall the number of vigorous bouts of physical activity/week performed rather than the details necessary to accurately calculate MET hours/week. Therefore, it was surprising that vigorous bouts of physical activity did not predict HRQL. However, one reason for this nonsignificant finding could be due to the fact that HRQL is a gross measurement and therefore, might not be a specific or sensitive enough measure in this study. Yet, it is more likely that the characteristics of the sample are driving these results. For example, the participants in this study scored above the mean on both the HRQL and CDQ, indicating, higher levels of HRQL than the normative comparison groups. The positive aspect of this finding is that it suggests that the CD patients who volunteered for this study were actually experiencing higher HRQL than anticipated. This sample was mostly recruited from national or local support groups and was most likely more active in coping with their disease. The sample was 72% women, which was similar to other research (Ciacci et al., 1995; Green, 2005; Green et al., 2001) and the pilot study (Barella et al., 2008), yet the sample, had higher GF diet adherence (i.e. all but 4 were at 100% adherence) than other research (Häuser et al., 2007). In fact, this CD sample is also high functioning in other areas, in that they have above average participation in both vigorous bouts of activity per week and MET hours, and had been on the GF diet for an average of approximately 7 years. Physical activity has been found to help populations who suffer from a chronic disease; however, those with physical

limitations from a chronic disease might be impacted more than this CD sample, who were not physically limited. These results indicate that there is not a strong relationship between vigorous bouts and HRQL when a high functioning CD sample is used.

The results for aerobic fitness and HRQL were also somewhat surprising in that correlational, cross-sectional and experimental studies that have assessed the relationship between aerobic fitness and HRQL in chronic disease populations have mostly shown positive relationships. For example, studies using Fibromyalgia patients (Mannerkorpi et al., 2000) and Multiple Sclerosis patients (Sutherland et al., 2001), where aerobic fitness was manipulated using an exercise intervention, have supported a positive effect for the exercise group with HRQL. However, changes in aerobic fitness did not always predict changes in HRQL. For example, Rejeski et al. (1996) reported from their review that changes in a fitness parameter did not impact HRQL as much as performance based measures of dysfunction, while King et al. (1989) found that the change in  $VO_2$  max was not correlated with any of the other measures in their study except body weight.

The lack of significant results for functional fitness was also somewhat surprising. Functional fitness was an exploratory variable, and we did not have an *a priori* hypothesis; however, since functional status or functional fitness has been found to be positively associated with health-related quality of life in past research (Lord & Menz, 2002; Maly, Costigan, & Olney, 2006; Orfila et al., 2006; Ruhland & Shields, 1997; Sato, Kaneda, Wakabayashi, & Nomura, 2007; Wan et al., 1999), we did expect to find a positive relationship.

The non-significant results for MET hours/week were not surprising. First, MET hours/week was not found to be a positive predictor in our pilot study. Second, it has been suggested that MET hours/week is not as readily ascertained as is the number of vigorous bouts of physical activity/week (DiPietro et al., 1993). That is, MET hours/week might have more measurement error than vigorous bouts of physical activity/week since MET hours/week is comprised of three types of physical activity (exercise, household, and gardening) at varying intensities, with some of them also being less structured, while vigorous bouts of physical activity/week requires the recall of the more intense activities that might be more readily brought to mind (DiPietro et al., 1993; Matthews, 2002; Sallis & Saelens, 2000).

#### *Executive Function*

The canonical correlations for executive function with MET hours/week and aerobic fitness were not significant. However, the canonical correlation for the executive function composite with vigorous bouts of physical activity/week and functional fitness were statistically significant. The non-significant results for MET hours/week were not surprising for similar reasons as described previously. That is, MET hours/week was not a predictor in our previous pilot study, nor has it been shown to be an accurate predictor in past literature due to recall error.

The results for aerobic fitness were somewhat surprising, in that aerobic fitness, usually predicts cognition in correlational studies; however, when tested in experimental designs, it has not always been found to be the main mechanism driving changes in cognitive function. Therefore, since our study was correlational in nature, it was

hypothesized that aerobic fitness would be a positive predictor of executive function. For example, Etnier et al. (1997) found strong relationships in correlational and cross-sectional studies ( $r=.53$ ), while an overall effect size of 0.18 was reported for randomized experimental designs. When correlational studies were examined alone, Etnier et al. (2006) reported a smaller positive relationship ( $r=.29$ ). However, the results of this current study do not provide a positive relationship for exercise and executive function. This could be due to the fact that aerobic fitness might not be the main mechanism behind changes in cognition. For example, Colcombe and Kramer (2003) did not find changes in  $VO_2$  max to significantly alter the effect size found for exercise on executive function. Our inability to find a positive relationship between aerobic fitness and executive function in this study could be due to the type of aerobic fitness test used; however, we don't believe that to be the case. The Rockport 1-mile walk estimates  $VO_2$  max based on mile walk time, gender, heart rate at completion of walk, and age of participant. All of these factors contribute to reliability of the instrument in its prediction of  $VO_2$  max, yet, it is not flawless in its estimation of  $VO_2$  max. However, Colcombe et al. (2004) tested the reliability of the Rockport, by assessing the  $VO_2$  max obtained from a maximal bout on a treadmill in a sub group of participants, and reported a high correlation with the Rockport 1-mile walk, thus providing confidence to us about its reliability. Further, other correlational studies have also used sub-max measures of fitness, such as body fat, body mass, and lung function (Bunce, 2001; Bunce & Birdi, 1998; Bunce, Warr, & Cochrane, 1993), pulmonary function measures (Etnier et al., 1999), and a 6-minute walk (Etnier et

al., 1999; Lord & Menz, 2002) and were able to find a positive relationship between aerobic fitness and cognitive performance.

The significant results for vigorous bouts of physical activity/week indicate that it might be a variable that is an important predictor for a variety of reasons. First, in studies that have assessed physical activity prospectively through self-report measures, they have found physical activity to be positively related to cognitive function. Although, most of these studies have not examined relationships for the individual components of physical activity (i.e., frequency, duration, intensity), general conclusions drawn from these studies are important because they all indicate that something about physical activity (type of exercise, kilocalories expended, minutes exercised) is important for cognitive function. For example, most of the prospective studies that have examined cognitive performance outcomes support the benefits of physical activity on cognition (Albert et al., 1995; Barnes, Yaffe, Satariano, & Tager, 2003; Lytle, Vander Bilt, Pandav, Dodge, & Ganguli, 2004; van Gelder et al., 2004). Further, when clinical outcomes have been measured, such as dementia risk (Abbott et al., 2004; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), cognitive function in older women (Lindsay et al., 2002; Weuve et al., 2004) and Alzheimer's Disease (AD) (Lindsay et al., 2002; Wilson et al., 2002), all but Wilson et al. (2002) showed support for the benefits of physical activity.

From these studies, it has been made clear that physical activity is an important predictor of cognition; however, in our current study only vigorous bouts of physical activity/week, and not MET hours per/week predicted cognition. The results from our

current study are similar to those Angevaren et al. (2007) who found that average intensity of physical activity, and not total time or MET hours of physical activity was predictive of cognitive performance in cognitive tasks, such as processing speed, memory, mental flexibility, and overall cognition. Again, participants might be able to more accurately recall the number of vigorous bouts of physical activity/week performed than the details necessary to accurately calculate MET hours/week (DiPietro et al., 1993; Sallis & Saelens, 2000).

The number of vigorous bouts of physical activity per week is an important predictor of executive functioning for a couple of reasons. First, it has been shown that physical activity helps sustain or increase cognitive abilities (Albert et al., 1995; Barnes, Yaffe, Satariano, & Tager, 2003; Lautenschlager et al., 2008; Lytle, Vander Bilt, Pandav, Dodge, & Ganguli, 2004; van Gelder et al., 2004) and prevents clinical cognitive decline or decrease dementia risk (Abbott et al., 2004; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Lindsay et al., 2002; Podewils et al., 2005; Weuve et al., 2004).

There are mechanisms, such as, increases in cerebral blood flow, neurotransmitters, BDNF, and neural growth that are thought to explain why physical activity is beneficial for cognitive performance. Previous animal research supports the link between physical activity and new synapse creation and greater blood flow in the cerebral cortex (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990), increased expression of BDNF (Klintsova, Dickson, Yoshida, & Greenough, 2004), more synapses per neuron and Fos-positive cells (Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996), and neurogenesis and increased synaptic plasticity (Leal-Galicia, Castaneda-

Bueno, Quiroz-Baez, & Arias, 2008). Additionally, human studies support the link between physical activity and greater activation in brain regions associated with attentional control (Colcombe, Kramer, Erickson et al., 2004). Therefore, these proposed mechanisms in both animal and human studies provide potential reasons for why physical activity, and specifically vigorous bouts of physical activity, is related to executive function.

The significant results for the relationship of functional fitness with executive function also support the belief that something other than aerobic fitness is responsible for the differences in cognitive function found. The TUG required participants to stand quickly from a seated position and walk, jog, or run as quickly as possible to a cone (10 feet from the chair), turn around and walk back. This test requires strength in their lower extremities (stand up), a quick burst of speed (get to the cone), agility (stop at the cone, or turn the cone), and balance (sit back down). This test might be a more meaningful predictor of cognitive performance than aerobic fitness because it takes into account multiple measures of fitness (strength, flexibility, anaerobic power). In addition, the instructions, behavior, and functions of this TUG test require executive processes, such as planning, decision-making, goal setting, initiating a behavior, self-evaluation, and altering the behavior, if needed. Participants also use other executive functions, such as inhibition (to block out distractions), working memory (to update and store the directions), and attentional capacity to complete the TUG (Salthouse et al., 2003). Thus, the observed relationship is logical given the need to access executive function resources to complete the TUG task.

### *Limitations*

One limitation of this study was that a correlational design was used. Thus, the results of the study do not establish a cause-and-effect relationship between physical activity, functional fitness and executive function. However, this study did provide external validity and identification of these relationships and lays the groundwork for future studies using an experimental design to test cause-and-effect relationships.

A second limitation is that random sampling was not used and the study sample may not be representative of the general population of CD patients. That is, our CD sample had better HRQL when compared to the normative groups, and is likely a very high functioning sample of CD patients.

A third limitation was the use of the canonical correlations for the statistical analyses. The canonical correlation analysis was determined to be the best statistical tool for this data, given that there was an interest in determining the relationships between individual predictor variables and sets of dependent variables. Multiple regression could have been chosen if there was a many-to-one relationship (many predictors to one dependent), but the hypotheses that were developed *a priori* led us to choose a statistical analysis tool that would analyze and determine a one-to-many relationship. That is, we were interested in determining the relationship of each of our predictor variables with HRQL and Executive Function. Since this was the first study to assess these relationships, hypotheses were developed around the larger constructs, HRQL and Executive Function, and predictions were not made about individual subscales or tests. HRQL consisted of both the SF-36 measure, as well as the CDQ, giving us a total of 15

variables. Executive function consisted of six main variables. Therefore, this canonical correlation analysis allowed variates or composites of both HRQL and Executive function to be created and correlated with each of the predictors. However, as previously described, when a canonical correlation is used, it is not possible to identify the specific individual relationships. Thus, the use of this analysis is limiting in that it makes it difficult to determine the importance of each variable that composed the composite, as well as to draw conclusions about the overall direction of the relationships that were found. Therefore, future studies will need to consider the limitations of using a canonical analysis.

#### *Future Direction*

CD impacts 1 in 131 people in the United States and is associated with lower levels of HRQL and cognitive functioning. Physical activity and aerobic fitness have been found to positively predict HRQL and cognition, yet those relationships had not been investigated in CD patients. Therefore, this study has made an important contribution to the literature by investigating these relationships in this population. This study found that number of vigorous bouts of physical activity/week and functional fitness were statistically significant positive predictors of the executive function composite. These findings are important for a couple of reasons. First, this is the first study to show established positive relationships between physical activity and executive function in CD patients. Second, this study provides preliminary support for these positive relationships and suggests the need to use interventions to determine the potential causal relationship between physical activity and executive function. Third, to

determine if aerobic fitness is an important variable of interest, it will be important to not only measure aerobic fitness at one time point, but to also assess how changes in aerobic fitness impact HRQL and executive function. Future research may also want to use similar executive function tests; however, the CLOX test and the MMSE are not recommended, unless the subject sample is known to have dementia or severe cognitive impairment. This recommendation stems from a limited range of responses on both tests, indicating both high and homogeneous scores. This problem could also be solved by including a more representative sample of CD patients. This representative sample may provide a larger range of scores on the cognitive tests mentioned above, and also on the HRQL measures, since our current sample had scores better than the norms for most of the outcome measures.

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## APPENDIX

### APPENDIX A: CONSENT FORM

Consent to Act as a Human Participant: Long Form

#### UNIVERSITY OF NORTH CAROLINA AT GREENSBORO

THIS IS A TEMPLATE FOR THE LONG FORM FOR OBTAINING INFORMED CONSENT FOR PARTICIPATION IN RESEARCH. IT MUST BE ADAPTED TO INCLUDE ALL OF THE INFORMATION REQUIRED FOR INFORMED CONSENT. IF AN ITEM IS NOT APPROPRIATE FOR THE STUDY, PLEASE DELETE IT FROM THE FORM.

#### CONSENT TO ACT AS A HUMAN PARTICIPANT: LONG FORM

Project Title: The influence of physical activity and aerobic fitness on health-related quality of life (HRQL) and cognitive performance in Celiac Disease (CD) patients.

Project Director: Lisa A. Barella

Participant's Name: \_\_\_\_\_

#### DESCRIPTION AND EXPLANATION OF PURPOSE AND PROCEDURES:

Lisa A. Barella, a doctoral student in the Exercise and Sport Science Department, has requested your participation in a research study at this institution. The title of the research is **The influence of physical activity and aerobic fitness on HRQL and cognitive performance in CD patients.**

The purpose of the research is to identify the degree to which physical activity status and aerobic fitness are related to HRQL and cognitive performance in CD patients.

You will be asked to provide your informed consent to participate. You will be asked to fill out several questionnaires and to perform cognitive testing, a functional fitness test, and an aerobic fitness test. The aerobic fitness test and the functional fitness test will be conducted either inside or outside. During the functional fitness test, you will be asked to rise from a chair with arm rests, walk 3 meters, turn 180 degrees, return to the chair, and sit down. During the aerobic fitness test, you will be asked to walk as fast as you can for one mile or until you ask for the test to stop. After completion of the aerobic fitness test you can walk to cool down for approximately 5 minutes. The testing will be done following the guidelines of the American College of Sports Medicine. The amount of time required is approximately two hours per testing session.

There are no feasible alternative procedures available for this study.

You are free to refuse to participate or to withdraw your consent to participate in this research at any time without penalty or prejudice. Your participation is entirely voluntary. You are also encouraged to ask questions at any time.

**RISKS AND DISCOMFORTS:**

There are minor risks that are possible as a result of participating in this study. These include muscle fatigue and dizziness during and after the exercise, abnormal changes in heart function, and, in very rare instances, heart attack (non-fatal or fatal) may also occur during the exercise test. However, the American College of Sports Medicine (2006) has provided the following information regarding this risk: The incidence of sudden cardiac death during vigorous exertion in healthy adults is estimated at one death per year for every 15,000 to 18,000 individuals. The overall risk of exercise testing in a mixed subject population is approximately six cardiac events (e.g. heart attack, dangerous irregular heartbeat, or death) per 10,000 tests. These are all conditions that would require immediate medical attention. In the unlikely event of an emergency, the experimenter will provide Cardio-Pulmonary Resuscitation (CPR) and/or administer an Automatic External Defibrillator (AED) if appropriate and will call 911 for emergency assistance.

**POTENTIAL BENEFITS:**

The direct benefit that you will receive from this study is that you will be informed of your estimated aerobic fitness level. The indirect benefits are that this research will help the researchers gain an understanding of the relationship between physical activity, aerobic fitness, and the dependent variables (HRQL and cognitive performance). The results of the research study may be published but your name will not be revealed. In order to maintain confidentiality, the investigators (Dr. Etnier and Lisa A Barella) will substitute your name with a code number. Data will be stored in a locked office in the Exercise and Sport Psychology Lab in the Health and Human Performance Building at the University of North Carolina at Greensboro. Data will be destroyed via shredding after publication (anticipated to be 2011). Electronic data relevant to this study may be stored indefinitely, but will be free of personal identifiers.

There is no compensation for participation in this study; however, upon completion of the study, a small donation will be made to the Gluten Intolerance Group in your name, or anonymously, if that is your preference.

**COMPENSATION/TREATMENT FOR INJURY:**

There is no compensation for any physical or psychological events that may result from your participation. Please contact Mr. Eric Allen at (336) 256-1482 if you sustain any research-related injuries.

**CONSENT:**

By signing this consent form, you agree that you understand the procedures and any risks and benefits involved in this research. You are free to refuse to participate or to withdraw your consent to participate in this research at any time without penalty or prejudice; your participation is entirely voluntary. Your privacy will be protected because you will not be identified by name as a participant in this project.

The University of North Carolina at Greensboro Institutional Review Board has approved the research and this consent form. The University of North Carolina at Greensboro Institutional Review Board insures that research which involves people follows federal regulations. Questions regarding your rights as a participant in this project can be answered by calling Mr. Eric Allen at (336) 256-1482. Questions regarding the research itself will be answered by Lisa Barella by calling (336) 253-5539. Any new information that develops during the project will be provided to you if the information might affect your willingness to continue participation in the project. You will be offered a copy of this consent form.

By signing this form, you are affirming that you are 18 years of age or older and are agreeing to participate in the project described to you by Dr. Jennifer Etnier or Lisa A. Barella.

\_\_\_\_\_  
Participant's Signature

\_\_\_\_\_  
Date

## APPENDIX B: GENERAL DEMOGRAPHIC AND HEALTH STATUS QUESTIONNAIRE

### General Demographic and Health Status Questionnaire



Date: \_\_\_/\_\_\_/\_\_\_

Identification Number: \_\_\_\_\_

### General Demographic and Health Status Questionnaire

**Directions:** This questionnaire asks about demographic information, along with your current and past health status. Please answer as accurately as possible. Please check “X” in the correct or write in a specific answer when asked.

1). Gender

Male                      Female

2). Date of Birth: \_\_\_/\_\_\_/\_\_\_      Age (in years) \_\_\_\_\_

3). Marital Status:

Single    Married/Partnered              Separated              Divorced              Widowed

4). Highest Level of School Completed:

Grade School  
High School  
2-year Technical School/2-year Associate Degree  
Bachelor’s Degree  
Masters Degree  
Doctoral (PhD/PsyD/MD/EdD)

5). Do you have Celiac Disease?

NO              YES

a). If, NO, stop completing this questionnaire

Identification Number: \_\_\_\_\_

6). Were you diagnosed with Celiac Disease with a **Biopsy?**

NO YES

a). If, NO, How were you diagnosed? \_\_\_\_\_

7). What was the date of your diagnosis? \_\_ \_\_/\_\_ \_\_/\_\_\_\_

8). Are you currently (within the past 2 weeks) adhering to a gluten free diet?

NO YES

**(If, NO, proceed to Q#9)**

**(If, YES, skip Qs#9, 10 and 11; proceed to Q#12)**

-----QUESTIONS FOR THOSE WHO ARE NOT ADHEREING TO A GLUTEN-FREE DIET-----  
-----

9). If, NO to question #8, why are you NOT adhering to the gluten free diet? \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

10). If, NO to question #8, did you adhere to the gluten free diet in the past?

NO YES

a). If YES, when did you **start** the gluten free diet? \_\_ \_\_/\_\_ \_\_/\_\_\_\_ and when  
did you **end** the gluten free diet? \_\_ \_\_/\_\_ \_\_/\_\_\_\_

b). **If NO to question #10, skip Q#11; proceed to Q#14**

Identification Number: \_\_\_ \_\_\_ \_\_\_ \_\_\_

11). When you were adhering to the gluten free diet in the past, how would you rate your adherence?

All of the time, 100% adherence; I never intentionally ate anything with gluten; I checked all foods very carefully

Almost all of the time, 90% adherence; I rarely ever ate anything with gluten, but about 10% of the time I would consume foods with gluten

Most of the time, 75% adherence; I usually ate gluten free; Occasionally, I allowed myself to consume foods with gluten. This occurred about 25% of the time

Some of the time, 50% Adherence; I ate gluten free foods 50% of the time; however, during the other 50%, I ate foods with gluten

A little of the time, 25% Adherence; I ate foods with gluten mostly; Once in awhile, I tried to eat gluten free foods

None of the time, 0% Adherence: I never ate gluten free foods

**Now, SKIP to Question #14**

-----QUESTIONS FOR THOSE WHO ARE ADHEREING TO A GLUTEN-FREE DIET-----

12). When did you start adhering to the gluten free diet?

Date: \_\_\_ \_\_\_/\_\_\_ \_\_\_/\_\_\_ \_\_\_ \_\_\_

13). How would you rate your current (within the past 2 weeks) adherence to the gluten free diet?

All of the time, 100% adherence; I never intentionally eat anything with gluten; I check all foods very carefully

Almost all of the time, 90% adherence; I rarely ever eat anything with gluten, but about 10% of the time I consume foods with gluten

Most of the time, 75% adherence; I usually eat gluten free; I occasionally allowed myself to consume foods with gluten about 25% of the time

Some of the time, 50% Adherence; I eat gluten free foods 50% of the time; during the other 50%, I eat foods with gluten

A little of the time, 25% Adherence; I eat foods with gluten mostly; Once in awhile, I try to eat gluten free foods

None of the time, 0% Adherence: I never eat gluten free foods

Identification Number: \_\_\_\_\_

14). Please rate how helpful your doctor was in explaining Celiac Disease to you when you were diagnosed?

Not at all	Slightly	Moderately	Quite a bit	Extremely
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

15). Do you currently see a medical doctor for Celiac Disease related issues?

NO YES

a). If NO, go to question #16

b). If YES, how would you currently rate your doctor's communication with you?

Poor	Fair	Good	Very good	Excellent
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

16). Were you referred to a nutritionist upon being diagnosed with Celiac Disease?

NO YES

a). If NO, go to question #19

b). If YES, did you have an appointment or consultation with the nutritionist?

NO YES

a). If NO, go to question #19

b). If YES, please answer questions #17 + #18

Identification Number: \_\_\_\_\_

17). How satisfied were you with the services that the nutritionist offered with regards to the Gluten Free Diet?

Not at all	Slightly	Moderately	Quite a bit	Extremely
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

18). Were there any specific areas that you were dissatisfied with when consulting with the nutritionist?

NO      YES

a). If YES, please list: \_\_\_\_\_

\_\_\_\_\_

19). What physical/bodily symptoms did you experience prior to your diagnosis with Celiac's Disease?

\_\_\_\_\_

\_\_\_\_\_

20). What mental or cognitive symptoms did you experience prior to your diagnosis with Celiac Disease?

\_\_\_\_\_

\_\_\_\_\_

Identification Number: \_\_\_\_

21). If you adhere to the gluten free diet (either currently or in the past), did the diet help relieve any of your previous symptoms?

NO YES

If YES, what symptoms were alleviated? \_\_\_\_\_

\_\_\_\_\_

If NO, what symptoms were still present after being on the gluten free diet for at least 6 months?

List Symptoms: \_\_\_\_\_

\_\_\_\_\_

This Question is Not Applicable; I was never on the gluten free diet for 6 months or MORE

22). Other than Celiac Disease, do you have any other autoimmune diseases?

NO YES

If, YES, please list: \_\_\_\_\_

\_\_\_\_\_

23). Other than Celiac Disease do you have any other diseases (anemia, osteoporosis, thyroid)?

NO YES

If, YES, please list: \_\_\_\_\_

\_\_\_\_\_

Identification Number: \_\_\_\_

24). Do you have any other medical complaints, problems, or disorders?

NO YES

If, YES, Please list: \_\_\_\_\_

\_\_\_\_\_

25). Are you currently taking any medications?

NO YES

If, YES, please list: \_\_\_\_\_

\_\_\_\_\_

26). Are you currently (within the past 2 weeks) physically active?

NO YES

If, YES, please list type of activity: \_\_\_\_\_

If, YES, please list the typical number of sessions per week of the activity: \_\_\_\_

If, YES, please list the typical duration of the activity: \_\_\_\_\_(minutes)

(Note: if you participate in MORE than ONE activity, please feel free to list the OTHER activities in the remaining space below and use more space on the back of this sheet if necessary)

Identification Number: \_ \_ \_ \_ \_

Activity #2

If, YES, please list type of activity: \_\_\_\_\_

If, YES, please list the typical number of sessions per week of the activity: \_\_\_\_\_

If, YES, please list the typical duration of the activity: \_\_\_\_\_ (minutes)

Activity #3

If, YES, please list type of activity: \_\_\_\_\_

If, YES, please list the typical number of sessions per week of the activity: \_\_\_\_\_

If, YES, please list the typical duration of the activity: \_\_\_\_\_ (minutes)

27). Are you interested in being contacted about the results of this study? (Upon receipt by the investigators, this information will be stored separately from the questionnaire responses and will not be tied to your data).

NO      YES

If YES, what is your name: \_\_\_\_\_

If, YES, please list your telephone number: \_\_\_\_\_

If YES, please list your email (if you have one): \_\_\_\_\_

21). Is there anything else that you would like to mention? \_\_\_\_\_

\_\_\_\_\_

Thank you for completing the survey! We really appreciate your help!

For UNCG Use Only: Certification ID of person entering this form: \_ \_ \_ \_ \_

Date Entered: \_\_ \_\_/\_\_ \_\_/\_\_\_\_