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The purpose of this study was to determine the relationship between a number of factors including cognitive performance and quality of life (QOL), premorbid Verbal IQ and QOL, cognitive performance and premorbid Verbal IQ, and length of time since COVID-19 diagnosis and QOL. In addition, to evaluate whether cognitive performance and premorbid Verbal IQ predict QOL based on perception of cognitive function or one's well-being in a group of non-hospitalized individuals at least 12 weeks post COVID-19 diagnosis.

Twenty-three participants completed the remote study protocol procedures. The protocol consisted of the following tasks: 1. a participant intake form, 2. the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) Version 4, 3. the Lexical Orthographic Familiarity Test (LOFT), 4. a QOL measure based on emotional health (Neuro-QOL Item Bank v1.0: Positive Affect and Well-Being), and one based on cognitive health (Neuro-QOL Item Bank v2.0: Cognitive Function). The main outcome variables included: the ImPACT Two-Factor Memory and Speed Composites, the LOFT raw score, and T-scores from each QOL measure. A multiple linear regression was used to determine the effect of the Speed Composite from the ImPACT and the LOFT raw score on outcomes from each measure of QOL. A multiple linear regression was also used to determine the effect of the Memory Composite from the ImPACT and the LOFT raw score on outcomes from each measure of QOL. Pearson's correlations were used to determine the relationship between the following: each QOL measure and both the Memory Composite and Speed Composite from the ImPACT, each QOL measure and the LOFT raw score, the LOFT raw score and both the Memory Composite and Speed Composite from the ImPACT, and each QOL measure and days since COVID-19 diagnosis.

Findings revealed small-medium positive relationships between cognition and QOL, a small positive relationship with QOL in the cognitive domain and premorbid Verbal IQ, a small positive relationship between premorbid Verbal IQ and objective memory performance, and a small negative relationship between QOL in the emotional domain and length of time since COVID-19 diagnosis. A majority of the relationships lacked statistical significance. Premorbid Verbal IQ and cognitive performance measured via Speed Composite scores, with outliers included in analysis, predicted QOL in the cognitive domain. No additional predictor models for QOL reached significance. Results must be interpreted with caution given the small sample size ($n = 23$).

Relationships between outcome variables varied based on the QOL measure used and the cognitive area assessed. Given findings, clinicians are encouraged to include a measure of speed performance (i.e., reaction time) when assessing cognitive function in individuals following COVID-19 despite hospitalization status. In addition, providing QOL measures to patients presenting with cognitive deficits may reveal functional impairments. Additional research is needed to better understand the long-term impact of COVID-19 on cognition and QOL.

THE LONG-TERM IMPACT OF COVID-19: UNVEILING THE RELATIONSHIP
BETWEEN COGNITION AND QUALITY OF LIFE

by

Brooke E. Holt

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Approved by

Dr. Kristine Lundgren
Committee Chair

DEDICATION

My dissertation is dedicated to my son, Weston. I hope you always pursue your dreams.

APPROVAL PAGE

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

Committee Chair

Dr. Kristine Lundgren

Committee Members

Dr. Hiram Brownell

Dr. Reva Klein

Dr. Kim McCullough

Dr. Jessica Obermeyer

June 13, 2022

Date of Acceptance by Committee

June 13, 2022

Date of Final Oral Examination

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CHAPTER I: INTRODUCTION

According to the World Health Organization (2022), “Coronavirus disease (COVID-19) is an infectious disease caused by the SARS- CoV-2 virus” (para. 1). Given COVID-19 is highly transmissible, in spring 2020, COVID-19 quickly spread across the United States and around the world resulting in a pandemic (WHO, 2020b). In the US, there have been 82,196,077 cases of COVID-19 and 996,653 deaths from January 21, 2020, to May 13th, 2022 (CDC, 2022a). The high number of total cases of COVID-19 (CDC, 2022a) is concerning given the acute and long-term consequences associated with this disease.

A wide range of symptoms have been associated with COVID-19, including neurological symptoms. Multiple studies have documented cognitive consequences associated with COVID-19 (Alemanno et al., 2021; Almeria et al., 2020; Graham et al., 2021; Negrini et al., 2020; Raman et al., 2021; Woo et al., 2020; Zhou et al., 2020). Most of the literature reporting neurological or cognitive consequences associated with COVID-19 have included individuals who have been hospitalized (Alemanno et al., 2021; Almeria et al., 2020; Carfi et al., 2020; Helms et al., 2020; Liotta et al., 2020; Negrini et al., 2020; Ora et al., 2020; Raman et al., 2021; Zhou et al., 2020). However, recent literature suggests potential for persistent cognitive sequela in non-hospitalized individuals following COVID-19 (Ceban et al., 2022; Graham et al., 2021). In addition, reduced quality of life (QOL) has been reported in non-hospitalized individuals outside of the acute phase of disease progression (Graham et al., 2021; Tabacof et al., 2022).

Understanding what factors impact a person’s day-to-day life during and after a pandemic is particularly important. The pandemic led to a sudden onset of stay-at-home orders resulting in businesses closing, travel ceasing, and most people working from home. Parents often had to

balance work and childcare, while also facilitating their children's studies from home as schools across the US transitioned to remote learning. All these changes occurred in a relatively short time, causing everyday lives of many Americans across the US to dramatically shift. While pandemic related circumstances may affect QOL, QOL may also be directly affected by acute and/or long-term consequences of COVID-19. Additional factors such as premorbid Verbal IQ may impact QOL as well.

Limited studies have been conducted exclusively in a non-hospitalized COVID-19 positive cohort in the chronic phase of the disease with recruitment conducted from the community. To our knowledge, no studies have reported on the cognitive consequences and the subsequent impact on QOL in this specific population. Additional research is warranted to determine the relationship between current cognitive performance, QOL, and premorbid Verbal IQ. These findings may provide a more comprehensive understanding of cognition and QOL changes following COVID-19. In addition, they have the potential to inform clinical practice to optimize functional outcomes.

The present study aims to determine the relationship between a number of factors including cognitive performance and QOL, premorbid Verbal IQ and QOL, cognitive performance and premorbid Verbal IQ, and length of time since COVID-19 diagnosis and QOL. In addition, this study aims to determine if cognitive performance and premorbid Verbal IQ predict QOL in either the cognitive or emotional domains in individuals at least 12 weeks post COVID-19 diagnosis who were not hospitalized due to COVID-19.

It was hypothesized there would be a strong positive relationship between cognitive performance, as measured by the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) Two-Factor score (Memory Composite and Speed Composite), and QOL in both

cognitive and emotional domains, as determined by the Neuro-QOL Cognitive Function and Neuro-QOL Positive Affect and Well-Being measures. Similarly, a positive relationship was hypothesized between premorbid Verbal IQ, as measured by the Lexical Orthographic Familiarity Test (LOFT) raw score, and QOL in both domains assessed. No relationship was expected between QOL in both domains assessed and time since COVID-19 diagnosis. A positive relationship was hypothesized between cognitive performance and premorbid Verbal IQ. In addition, we hypothesized cognitive performance, as measured by the ImPACT Two-Factor score (Memory Composite and Speed Composite), and premorbid Verbal IQ, as measured by the LOFT, to predict QOL in both domains assessed.

Determining the relationship between cognitive function in specific areas (i.e., Memory and Speed) and their effect on QOL in different domains (i.e., emotional versus cognitive domains) can provide a greater understanding of specific cognitive sequelae associated with COVID-19 and their impact on an individual's day to day life. In addition, determining the relationship between objective cognitive function and subjective QOL may reveal information regarding an individual's insight into deficits. These findings have the potential to inform assessment and treatment of cognitive impairment following COVID-19.

CHAPTER II: LITERATURE REVIEW

Overview: Coronavirus Disease 2019

According to the Centers for Disease Control and Prevention (CDC, 2021), “[Coronavirus disease 2019] COVID-19 is a respiratory disease caused by [severe acute respiratory syndrome coronavirus-2] SARS-CoV-2, a coronavirus discovered in 2019” (para. 1). COVID-19 was brought to the WHO’s attention on December 31, 2019, due to cases in Wuhan, China, and was subsequently labeled a pandemic on March 11th, 2020 (WHO, 2020b). While the definitive origin of COVID-19 is unknown, international scientists ranked potential causes, revealing the following: (a) origin from an intermediary host was deemed likely to very likely, (b) origin from direct zoonotic introduction was deemed possible to likely, (c) origin from cold/food chain items was deemed possible, and (d) origin from a laboratory was deemed extremely unlikely (WHO, 2021c). Despite COVID-19 having an unknown origin, both the World Health Organization (WHO) and Centers for Disease Control (CDC) have released information regarding how COVID-19 spreads.

COVID-19 is highly transmissible and may spread from respiratory passages secondary to sneezing or coughing (WHO, 2022). While COVID-19 spreads primarily via droplets, transmission can also be aerosolized (Oberfeld et al., 2020). The CDC (2020) specifies transmission is most likely to occur secondary to respiratory droplets from individuals in close proximity; however, the spread of COVID-19 may also occur via airborne transmission or via touching contaminated objects or surfaces. Lastly, while rare, COVID-19 has a low risk of transmission from animals to humans (CDC, 2020).

Individuals with COVID-19 may be asymptomatic or display symptoms varying in severity from mild to severe (CDC, 2021). Refer to Table 1 for a description of the different

severities of SARS-CoV-2. However, it is important to note that there are various clinical guidelines; therefore, the definitions for each level of severity may vary between clinical trials (NIH: COVID-19 Treatment Guidelines, 2021). Asymptomatic cases, in addition to the incubation period, have likely exacerbated the spread of COVID-19. Understanding how COVID-19 is transmitted between individuals is critical to control the spread of this highly transmissible disease. Despite stay-at-home orders and social distancing guidelines implemented across the United States (US), COVID-19 has had a devastating impact.

Table 1. SARS-CoV-2 Severity Categories with Descriptions from the NIH

Severity Category	Description
Asymptomatic or Presymptomatic infection	“Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19.”
Mild illness	“Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.”
Moderate illness	“Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO ₂) ≥94% on room air at sea level.”
Severe illness	“Individuals who have SpO ₂ <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO ₂ /FiO ₂) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.”
Critical illness	“Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.”

Note. Severity categories and descriptions are from NIH: COVID-19 Treatment Guidelines (2021).

Given the ease of transmission, COVID-19 has caused significant mortality and morbidity (Oberfeld et al., 2020). In the US, there have been 82,196,077 cases of COVID-19 and 996,653 deaths from January 21, 2020, to May 13th, 2022 (CDC, 2022a). Weekly cases in the US continue to accumulate in large numbers (CDC, 2022a). As of May 13th, 2022, within the past 7

days, there were 611,680 cases of COVID-19 in the US (CDC, 2022a). Given the case numbers of COVID-19, it is important to understand the symptoms associated with this disease.

Many different symptoms have been associated with COVID-19. A living systematic review on articles published prior to March 17th, 2021, with individuals 12 or more weeks following COVID-19 found more than 60 signs and symptoms recorded (Michelen et al., 2021). The WHO (2020a) provide a list of more than 20 symptoms, reporting fever, fatigue, and dry cough as the most frequently occurring symptoms (WHO, 2020a). Symptoms vary and may include nasal congestion, skin rash, conjunctivitis, and/or vomiting (WHO, 2020a). The WHO estimates approximately 80% of individuals with COVID-19 symptoms recover without seeking hospital care. However, “about 15% become seriously ill and require oxygen and 5% become critically ill and need intensive care” (WHO, 2020a). Regardless of history of hospitalization for COVID-19 symptoms, individuals may experience persistent symptoms which may include neurological symptoms (WHO, 2020a).

Neurological consequences from COVID-19 may occur in the acute or post-acute phases (Nath & Smith, 2021). The National Institute for Health and Care Excellence (2020c) define acute COVID-19 as “signs and symptoms of COVID-19 for up to 4 weeks”, ongoing symptomatic COVID-19 as “signs and symptoms of COVID-19 from 4 to 12 weeks”, and post-COVID-19 syndrome as “signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis”. However, the NIH COVID-19 Treatment Guidelines (2021) highlight, “To date, no case definition and no specific time frame have been established to define the syndrome of persistent symptoms and/or organ dysfunction after acute COVID-19”. Terminology has included, but is not limited to, the following: post-COVID-19 condition, long

COVID, and post-acute sequelae of COVID-19 (PASC) (NIH COVID-19 Treatment Guidelines, 2021). In addition, individuals impacted have been described as *long-haulers* (NIH COVID-19 Treatment Guidelines, 2021). Despite variations in terminology, the term *post COVID-19 condition(s)* has been used by the CDC (2022b) and WHO (2021a); however, definitions of the term vary. Through use of Delphi methodology, the WHO (2021a) reports the following clinical case definition:

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time. (para. 2)

In contrast, the CDC uses the terminology *post-COVID conditions* to encompass symptoms experienced four or more weeks following COVID-19 (2022b). Regardless of various nomenclature used, the potential long-term impact from symptoms following COVID-19 is concerning. The Americans with Disabilities Act (ADA) has even reported *Long COVID* may be classified as a disability (CDC, 2022b as cited from U.S. Department of Health and Human Services: Office for Civil Rights, 2021).

Cognitive Consequences Associated with COVID-19

Initially, COVID-19 was viewed as a virus impacting the respiratory system, not having a large impact on the nervous system, including the brain (Josephson & Kamel, 2020). However, findings from Mao et al. (2020) shifted perspectives as they reported neurological consequences

secondary to COVID-19 (as cited from Josephson & Kamel, 2020). Mao et al. (2020) conducted a retrospective case series using individuals hospitalized with COVID-19 and found neurological manifestations in 36% of participants. A variety of neurological manifestations were found, such as dizziness, headache, and/or impaired consciousness, among other neurological symptoms (Mao et al., 2020). Since publication of this study in April of 2020, researchers have investigated the neurological and cognitive consequences of COVID-19 using various patient populations (i.e., hospitalized versus non-hospitalized) and various assessment tasks.

Initial COVID-19 literature reported neurological or cognitive consequences associated with COVID-19 in individuals who had been hospitalized (Alemanno et al., 2021; Almeria et al., 2020; Carfi et al., 2020; Helms et al., 2020; Liotta et al., 2020; Negrini et al., 2020; Ora et al., 2020; Raman et al., 2021; Zhou et al., 2020). In contrast, fewer studies have documented neurological or cognitive consequences exclusively in non-hospitalized individuals with COVID-19 (Ding et al., 2020; Graham et al., 2021) despite non-hospitalized individuals representing a large portion of individuals with COVID-19.

Severity of COVID-19 has varied across studies. Literature documenting cognitive consequences associated with COVID-19 have included individuals with mild and moderate (Woo et al., 2020), moderate to severe (Raman et al., 2021), and severe COVID-19 (Negrini et al., 2020). However, in each of these studies, different criteria were used to define COVID-19 severity. For example, Woo et al. (2020) utilized WHO criteria, Mao et al. (2020) utilized the American Thoracic Society guidelines for community-acquired pneumonia, and Liotta et al. (2020) utilized use of mechanical ventilation at the time of hospitalization as a measure to classify individuals into non-severe versus severe COVID-19.

Not all studies on cognitive consequences of COVID-19 have reported participants severity of the disease. For example, Almeria et al. (2020) evaluated participants at a hospital, however, the number of days hospitalized ranged from zero to 30, and 20% of participants had received care in the Intensive Care Unit. Therefore, participants likely represented a range of COVID-19 severity (Almeria et al., 2020). In addition, Ora et al. (2020) classified their participants as individuals with non-severe COVID-19 since individuals did not have respiratory distress or require non-invasive ventilation. However, participants were hospitalized in a respiratory unit.

The instruments used to assess cognition have varied as well. The instruments used include: Mini-Mental State Examination (Alemanno et al., 2021; Negrini et al., 2020), Frontal Assessment Battery (Negrini et al., 2020), Montreal Cognitive Assessment (MoCA) (Alemanno et al., 2021; Raman et al., 2021), Modified Telephone Interview for Cognitive Status (TICS-M) (Woo et al., 2020), Continuous Performance Test (Zhou et al., 2020), Sign Coding Test (Zhou et al., 2020), Digit Span Test (Zhou et al., 2020), Digits Forward and Backward (Almeria et al., 2020), and Trail Making Test (Almeria et al., 2020; Zhou et al., 2020). The National Institute for Health and Care Excellence has published guidance regarding identification of individuals with ongoing symptoms following acute COVID-19 (2020b) and assessment of symptoms following acute COVID-19 (2020a). These recommendations include consideration of utilizing a questionnaire to screen for symptoms along with clinical assessment during initial consultation (2020b), discussing how symptoms impact the individual's day to day life (2020a), discussing the emotional impact (2020a), and using a validated screening instrument for individuals with new cognitive symptoms to determine the impact and impairment following acute COVID-19 (2020a). Despite these recommendations and growing research documenting cognitive

consequences associated with COVID-19, there does not appear to be a widely accepted protocol of instruments utilized to screen or assess cognition in individuals with COVID-19.

Results of these investigations have revealed a variety of findings. For example, Negrini et al. (2020) reported general cognitive decline in 33% of participants with severe COVID-19 ($n = 9$) based on performance from the MMSE. These individuals performed poorly on measures of attention and calculation, short term memory, constructional praxia, and a written language task (Negrini et al., 2020). Similar findings were reported by Woo et al. (2020) in individuals who had mild to moderate COVID-19. When comparing results from the TICS-M, a screening questionnaire for mild cognitive impairment from individuals post-COVID-19 and controls, participants post-COVID-19 had significantly lower scores from the TICS-M, particularly in areas such as short-term memory, attention, and concentration/language (Woo et al., 2020). Neither age nor sex predicted cognitive deficits (Woo et al., 2020). Using similar analysis, when comparing individuals assessed approximately two to three weeks after COVID-19 infection to controls, investigators revealed individuals recovered from COVID-19 had deficits in sustained attention (Zhou et al., 2020). Supporting Negrini et al.'s (2020) findings, based on total MoCA scores, Raman et al. (2021) reported 28% of individuals with COVID demonstrated impairment. When comparing performance on the MoCA from individuals with COVID-19 versus controls, participants with COVID-19 demonstrated impairment in executive/visuospatial skills (Raman et al., 2021). Alemanno et al. (2021) administered the MMSE, MoCA, and other measures at time of admission to a rehabilitation unit and one month post hospital discharge. Participants were previously hospitalized and in the subacute phase (5-20 days post symptom onset). Cognitive deficits were observed in approximately 80% of participants (Alemanno et al., 2021). Age was significantly correlated with both MoCA and MMSE scores. Progression of cognitive deficits

varied based on the cognitive screener utilized. However, the total score from the MoCA one month post discharge was significantly higher when compared to the total score from admission.

Ferrucci et al. (2021) assessed cognition in hospitalized individuals on average 4.4 months post discharge ($n = 38$). Despite participants being hospitalized, they were from non-intensive COVID-19 units (Ferrucci et al., 2021). In addition, individuals did not complete the neuropsychological testing if they presented with dementia or global cognitive decline per the MoCA screener (Ferrucci et al., 2021). Cognitive assessment encompassed many tasks, some of which included the Symbol Digit Modalities Test, Paced Auditory Serial Addition Test, and Selective Reminding Test, and the Spatial Recall Test (Ferrucci et al., 2021). Additional instruments were provided as well. Findings revealed impairments in processing speed in 42% of participants and impairments in delayed verbal recall in 26% of participants (Ferrucci et al., 2021). Subjective report of reduced cognitive function was noted in 32% of participants.

Whiteside et al. (2021) investigated long term neurocognitive function through a case series using individuals with a history of severe COVID-19 who were currently in acute rehabilitation. Participants had severe symptoms associated with COVID-19, in addition to previous long-term stays in the intensive care unit. Instruments were administered via phone, impacting instruments and tasks used (Whiteside et al., 2021). Tasks included, but were not limited to: Wechsler Adult Intelligence Scale -IV (WAIS-IV) Vocabulary subtest, WAIS-IV Digit Span subtest, Hopkins Verbal Learning Test- Revised, Repeatable Battery for the Assessment of Neuropsychological Status Story Memory task, and verbal fluency tasks (letter and animal fluency) (Whiteside et al., 2021). Ultimately, all participants demonstrated multi-domain mild cognitive impairment (Whiteside et al., 2021). Impairments in encoding and verbal fluency were noted. Participants varied in performance when completing tasks assessing

attention/working memory, executive function, verbal memory/learning, and language (Whiteside et al., 2021). Similar findings were gleaned from an observational series using 59 patients who had acute respiratory distress syndrome secondary to COVID-19 who had been hospitalized (Helms et al., 2020). Neurologic findings were reported in 81% of participants at time of admission to the Intensive Care Unit or when the neuromuscular blocker, in addition to sedation, were not administered (67%) (Helms et al., 2020). Thirty-three percent of participants who had been discharged from the hospital, “had had a dysexecutive syndrome consisting of inattention, disorientation, or poorly organized movements in response to command” (Helms et al., 2020, para. 3). However, it must be noted that seven participants had a history of neurologic disorders such as mild cognitive impairment and/or transient ischemic attack (Helms et al., 2020) prior to the COVID-19 diagnosis. The investigators reported a relationship between acute respiratory distress syndrome secondary to COVID-19 and agitation/confusion, encephalopathy, and corticospinal tract signs (Helms et al., 2020). When interpreting these findings, it must be noted that the investigators warn, “data are lacking to determine which of these features are due to critical illness-related encephalopathy, cytokines, or the effect of withdrawal of medication, and which features were specific to SARS-CoV-2 infection” (Helms et al., 2020, para. 6).

When comparing individuals with COVID-19 who had neurological symptoms to individuals not experiencing these symptoms, neurological symptoms were associated with reduced performance in working memory (Almeria et al., 2020). Using similar comparisons, scores in memory coding, attention, complex working memory, processing speed, executive function, and global Cognitive Index were significantly lower in individuals with COVID-19 who had headaches versus those without (Almeria et al., 2020). Almeria et al. (2020) found that performance on cognitive tasks did not differ between individuals who reported cognitive

impairment (34% of participants) versus individuals who did not report cognitive impairment following COVID-19. This finding raises the question of insight into subtle deficits. Ultimately, risk factors for cognitive deficits included: neurological symptoms at the time of COVID-19 infection, diarrhea, and oxygen therapy (Almeria et al., 2020). Of note, individuals with self-reported cognitive impairments scored significantly higher on anxiety and depression measures (Almeria et al., 2020).

Michelen et al. (2021) conducted a living systematic review on studies that met the following primary criteria: peer reviewed, a minimum of 100 participants, participants had a positive COVID-19 diagnosis through laboratory results or a clinical diagnosis, and reported outcomes were a minimum of 12 weeks following the onset of COVID-19. While 39 studies met these criteria, meta-analysis was conducted on 32 studies to determine frequently reported signs and symptoms of long COVID (Michelen et al., 2021). Location of studies and age of participants varied. Analysis was also conducted to determine symptoms across settings: non-hospitalized populations (4 studies), hospitalized populations (26 studies), or a combination of both (9 studies) (Michelen et al., 2021). The following were the most frequently occurring symptoms across participants included in the meta-analysis on long COVID: weakness (41%), general malaise (33%), fatigue (31%), concentration impairment (26%), and breathlessness (25%) (Michelen et al., 2021, p. 7). When comparing hospitalized versus non-hospitalized individuals, there was a significant difference in reports of fatigue, breathlessness/exertional dyspnea, chest pain, 'other' respiratory symptoms, weight loss, tremors, smell disturbance, hair loss, and memory impairment. For each of these symptoms, except for chest pain and smell disturbance, hospitalized individuals experienced the symptom with significantly greater proportion than non-hospitalized individuals. Despite a significantly greater proportion of

hospitalized participants reporting memory impairment (35%) when compared to non-hospitalized individuals, 16% of non-hospitalized individuals reported memory impairment (Michelen et al., 2021). Despite this finding, it is important to note that a small number of studies were used in the meta-analysis when comparing reports of memory impairment: non-hospitalized ($n = 1$) and hospitalized ($n = 3$).

Schou et al. (2021) also conducted a systematic review looking at the psychiatric complications secondary to long-COVID and determined possible risk factors and underlying mechanisms. While this study reviewed literature reporting primary data pertaining to psychiatric symptoms following COVID, studies reporting neuropsychiatric manifestations (i.e., cognitive impairments) were included as well (Schou et al., 2021). The systematic review included 66 articles with various sample sizes ($n = 3$ versus $n = 266,586$), length of time since acute COVID-19, and varying hospitalization status among participants (Schou et al., 2021). However, most articles included hospitalized participants (Schou et al., 2021). Schou et al. found depression and/or anxiety to be the most prevalently documented psychiatric deficit despite findings ranging from no report of depression and/or anxiety to over 30% (Schou et al., 2021). Of studies documenting post-traumatic stress disorder (PTSD), PTSD was found to vary among participants from 7% to 43% (Schou et al., 2021). Reports of fatigue varied from no fatigue to fatigue being documented in 87% of participants, while sleep disturbances also ranged from having no difference between a control group to sleep disturbance occurring in 85% of participants (Schou et al., 2021). Multiple studies included in this review (27/66) documented cognitive outcomes (Schou et al., 2021). Underscoring the heterogeneity of literature, Schou et al. (2021) report “the results range from no cognitive impairments at 4 months follow-up (Mattioli et al., 2021) to a report of 78% of the patients experiencing impaired performance on at least on cognitive domain

3 months after clinical recovery (Mazza et al., 2021)” (p. 341). Consistent with previous literature discussed, cognitive deficits were documented in the following: concentration, attention, memory (general and short-term), language, praxis abilities, and encoding and verbal fluency (Schou et al., 2021). Schou et al. even highlighted that progression, or regression, of cognitive function has varied following COVID. Schou et al. reports findings from a large study by Al-Aly et al. (2021) ($n = 98,661$), “non-hospitalized patients showed increased incidence of neurocognitive disorders (Hazard Ratio 3.2), sleep disorders (HR 14.5), anxiety (HR 5.4), trauma and stress related disorders (HR 8.9). Further, patients exhibited an excess burden of malaise and fatigue (HR 12.6)” (Schou et al., 2021, p. 330). Overall risk factors for long-COVID appeared to include the following: sex (female), symptom duration, and severity of COVID (Schou et al., 2021).

Davis et al. (2021) utilized an extensive electronic survey with 257 questions to individuals with suspected or confirmed COVID-19. The survey aimed “to better describe the patient experience and recovery process in those with confirmed or suspected COVID-19 illness, with a specific emphasis on the Long COVID experience” (Davis et al., 2021, p. 1). It must be noted that inclusion/exclusion criteria did not control for comorbidities or pre-illness health symptoms experienced prior to COVID-19 infection. Analysis was completed using responses from individuals with symptoms persisting greater than 28 days (Davis et al., 2021). Participants either had a positive COVID-19 test ($n = 1020$), a negative COVID-19 test ($n = 923$) or did not have a COVID-19 test ($n = 1819$) (Davis et al., 2021). While most participants were from the United States (41%), participants were from 56 different countries (Davis et al., 2021). Fifty-seven percent of participants were non-hospitalized and 35% were not hospitalized but sought care in an urgent care or Emergency Room setting, while only 8% were hospitalized (Davis et

al., 2021). Results indicated that 92% of respondents had symptoms over 35 weeks. Sixty-five percent of respondents reported symptoms for a minimum of 180 days, while the rest of the participants either had recovered ($n = 233$) or completed the survey prior to being 180 days post initial illness (Davis et al., 2021). Of concern, the participants experiencing symptoms greater than 180 days reported experiencing an average of 14 symptoms 7 months post illness onset (Davis et al., 2021). While respondents reported experiencing 56 symptoms on average throughout illness duration, the most debilitating symptoms included: fatigue, breathing issues, and cognitive dysfunction (Davis et al., 2021). Reports of cognitive impairment were high among participants. Brain fog and cognitive dysfunction (i.e., reduced attention, executive function, etc.) were endorsed by 85% of participants. Davis et al. (2021) even found, “55.5% (52.5% to 58.8%) of month 7 respondents experienced cognitive dysfunction during month 7” (p. 10). Memory impairment was endorsed by 73% of participants (Davis et al., 2021). Subsequently, Davis et al. (2021) found: “50.5% (47.3% to 53.6%) of respondents with symptoms for over six months experienced memory symptoms in month 7” (p. 10). Despite a large percentage of participants endorsing cognitive impairment, brain MRIs were often unremarkable. For example, no abnormalities were found in 87% of brain MRIs from respondents who had imaging completed and endorsed cognitive dysfunction and/or memory impairment (Davis et al., 2021). Cognitive impairments were not the only symptoms frequently endorsed. Neurological symptoms, in addition to a variety of other symptoms, have been reported at high rates and are discussed below.

Neurological Symptoms and Manifestations in Individuals with COVID-19

In addition to subjective cognitive impairments secondary to COVID-19, Davis et al. (2021) also reported neurological symptoms secondary to COVID-19. Many participants

endorsed the following: sensorimotor symptoms (91%), sleep challenges (79%), headaches (77%), emotion and mood symptoms (88%), taste and smell symptoms (58%), impairment in speech and language (49%), and hallucinations (23%) (Davis et al., 2021). Sixty-five percent of participants endorsed symptoms “for at least six months” (Davis et al., 2021, p. 12). Of these individuals, the most frequently reported symptoms were a combination of neurological and systemic symptoms (Davis et al., 2021).

Ora et al. (2020) administered a structured interview to obtain information on the frequency of neurological symptoms in individuals with non-severe COVID-19 who had been hospitalized. Although additional procedures were administered and determination of neurological symptoms was not the primary aim of this study, 82% of participants endorsed neurological symptoms (Ora et al., 2020). When interpreting this finding, it is important to note that 64% of participants had underlying cardiac or cerebrovascular disease (Ora et al., 2020). Kacem et al. (2021) yielded similar findings despite using different methods and participants being primarily non-hospitalized. Kacem et al. (2021) conducted a retrospective observational study which aimed to determine the association between neurological symptoms and COVID-19 as well as the evolution of these symptoms in individuals with COVID-19 in Tunisia. Utilizing survey questionnaires administered via telephone, Kacem et al. (2021) reported that 72% of individuals with COVID-19, or family members of deceased patients with COVID-19 reporting on the patients’ behalf, experienced neurological symptoms (Kacem et al., 2021). Twenty-three percent reported neurological symptoms without reporting other symptoms (Kacem et al., 2021). Further analysis revealed the most frequent symptoms with neurological underpinnings were headache (41%), impairment in smell (38% with over half of these individuals being anosmic), impairment in taste (37% with over half of these individuals being ageusic), myalgia (37%), and

sleep disturbance (37%) (Kacem et al., 2021). Additional analysis revealed a significant relationship between neurological symptoms and local transmission, fever, and respiratory symptoms. Neurological symptoms were more commonly reported in addition to respiratory symptoms (Kacem et al., 2021). Surprisingly, respiratory symptoms and gastrointestinal symptoms predicted neurological symptoms (Kacem et al., 2021).

Liotta et al. (2020) also conducted a retrospective analysis, however, investigators reviewed medical records for data collection from 509 patients hospitalized in Illinois. Twenty-six percent of participants were classified as having severe COVID-19, while the remaining participants were classified as non-severe (Liotta et al., 2020). Eighty-two percent of patients experienced neurologic manifestations starting any time since the onset of COVID-19 (Liotta et al., 2020). The frequency of neurologic manifestations was lower during the onset of COVID-19 (42%), as well as at the time of hospital admission (63%) (Liotta et al., 2020). Despite using different methods, similarities and differences were noted when comparing frequent neurologic manifestations reported from Liotta et al. (2020) and Kacem et al. (2021). Similar to Kacem et al., Liotta et al. found myalgias in 45% of patients and headaches in 38% of patients. However, Liotta et al. (2020) also reported encephalopathy in 32% of patients, dizziness in 30% of patients, dysgeusia in 16% of patients, anosmia in 11% of patients, and fatigue in 79% of patients. When comparing individuals with neurologic manifestations to those without, surprisingly, patients with neurologic manifestations were significantly younger (Liotta et al., 2020). Further analysis revealed a significantly greater frequency of neurologic manifestations in patients who had experienced severe COVID-19, which the investigators report primarily being due to significantly more individuals with severe COVID-19 having encephalopathy (Liotta et al., 2020). However, it is important to highlight that despite a significantly greater frequency of

neurologic manifestations in patients who had experienced severe COVID-19, 79% of individuals with non-severe COVID-19 experienced neurologic manifestations at some point during this disease (Liotta et al., 2020).

Carfi et al. (2020) investigated long standing neurological (i.e., headache, dysgeusia, anosmia) and non-neurological (i.e., dyspnea, cough, diarrhea) symptoms in individuals with COVID-19 who were previously hospitalized ($n = 143$). Participants had been discharged from the hospital and were on average 60 days after initial COVID-19 symptoms (administration of procedures were an average of 36 days since discharge) (Carfi et al., 2020). A questionnaire was used to collect self-report symptoms at two time points: acute phase of COVID-19 and current symptoms (Carfi et al., 2020). Despite individuals being discharged from the hospital, 87% of participants reported one or more symptoms (Carfi et al., 2020). Of these individuals, 55% reported three or more symptoms (Carfi et al., 2020). Fatigue was the mostly frequently reported symptom after the acute phase of COVID-19 (Carfi et al., 2020). This study highlights the consequences of COVID-19 persisting outside the acute phase.

Ding et al. (2020) conducted an electronic survey through a longitudinal study with non-hospitalized individuals ($n = 153$) following COVID-19. Of note, only 11% of participants had symptoms lasting more than 8 weeks after symptom onset (Ding et al., 2020). Despite being non-hospitalized, neurological manifestations were reported in 78% of participants. Nervous system symptoms were reported in 78% of participants, with 47% of individuals reporting central nervous system symptoms and 69% of individuals reporting peripheral nervous system symptoms (Ding et al., 2020).

Similar to Ding et al. (2020), Stavem et al. (2021) conducted a survey in non-hospitalized individuals following COVID-19 diagnosis. More specifically, Stavem et al. utilized a cross

sectional survey. However, it should be noted that hospitalization status was defined as non-hospitalized if the individual was not hospitalized 22 days following their COVID-19 diagnosis. The survey was comprised of a checklist inquiring about comorbidities, symptoms experienced in the acute phase, and symptoms currently experienced following COVID-19 diagnosis (Stavem et al., 2021). The symptom checklist was comprised of 23 items which included items such as headache, loss/disturbance of taste, loss/disturbance of smell, and confusion/changed consciousness (Stavem et al., 2021). While their study included self-reported post-acute symptoms, the responses ranged from 41 days following symptoms onset to 193 days, with the median being 117 days (Stavem et al., 2021). In the post-acute phase, less than ten percent of respondents endorsed headaches and less than 5 percent endorsed confusion/changed consciousness (Stavem et al., 2021). Interestingly, more than half of the respondents endorsed having no symptoms at the time of survey completion (Stavem et al., 2021). Although, the findings revealed “persistent symptoms were common after COVID-19 in non-hospitalised patients and were related to the symptom load and number of comorbidities present during the acute phase” (Stavem et al., 2021, p. 407).

Similar to Stavem et al., Skaalum Petersen et al. (2020) used a questionnaire provided via phone interview to identify and rate symptoms mild to severe retrospectively from the acute phase of diagnosis, and current symptoms at various time points following the initial data collection. Follow up was discontinued “if a participant reported symptoms to have ceased at an assessment or reported symptoms to be stable at 2 consecutive assessment occasions, and more than 2 months had passed since the acute phase” (Skaalum Petersen et al., 2020, p. e4059). Of note, the sample included children, with parents reporting the symptoms. Additional data were collected as well, such as the fatigue impact scale. While most individuals were not hospitalized,

eight of the 180 participants in the Faroe Islands were hospitalized (Skaalum Petersen et al., 2020). The most frequently endorsed persistent symptoms included: fatigue, loss of smell and taste, and arthralgias (Skaalum Petersen et al., 2020). At the last point of data collection, approximately 7% of respondents endorsed ‘headache’ (Skaalum Petersen et al., 2020). In total, 53% of participants endorsed continuation of one or more symptoms, on average, 125 days following COVID-19 diagnosis (Skaalum Petersen et al., 2020). Skaalum Petersen et al. conclude, “Our results show it might take months for symptoms to resolve, even among nonhospitalized persons with a milder illness course in the acute phase” (p. e4063).

In addition, Klein et al. (2021) sought to determine symptoms over a 6-month period in Israeli patients with mild COVID-19. Of note, individuals who were asymptomatic or those with severe cases of COVID-19 were excluded from this study and mild COVID-19 included individuals showing “symptoms such as fever, cough or breathing difficulties along with epidemiologic reason...” (Klein et al., 2021, p. 770). Phone interviews were used to administer a questionnaire at various time points which included completion approximately 6 months after the first data collection was obtained (Klein et al., 2021). Similar to Skaalum Petersen et al. (2020), approximately half of the participants endorsed one or more symptom at the last point of data collection, with the most frequently reported being fatigue, alternations in smell and taste, and difficulty breathing (Klein et al., 2021). These findings add to the literature underscoring reports of the long-term impact of COVID-19 regardless of disease severity.

Graham et al. (2021) aimed to determine neurologic manifestations in COVID-19 “long haulers” who had not previously been hospitalized. Participants were grouped based on positive versus negative SARS-CoV-2 results (Graham et al., 2021). However, all participants had clinical manifestations of COVID-19 and met COVID-19 symptom guidelines from the

Infectious Diseases Society of America (Graham et al., 2021). Individuals with a negative SARS-CoV-2 test were suspected to have post-acute viral syndrome (Graham et al., 2021). Participants completed tasks, including assessment of working memory, executive function, processing speed, and attention and executive memory if they attended the assessment in-person instead of via televisit (Graham et al., 2021). Surprisingly, the median number of reported neurological symptoms secondary to COVID-19 was five symptoms (Graham et al., 2021). In addition, a minimum of four symptoms was reported by 85% of participants (Graham et al., 2021). Analysis of neurologic symptoms participants reported (positive and negative SARS-CoV-2 responses included) secondary to COVID-19 indicated the following: 81% of individuals reported “brain fog”, 68% reported headache, 60% reported numbness and/or tingling, 59% reported dysgeusia, 55% reported anosmia, and 55% reported myalgias (Graham et al., 2021). In addition, 85% of participants reported fatigue secondary to COVID-19 (Graham et al., 2021).

With regard to neurologic examination, 53% of the individuals tested had abnormal findings (Graham et al., 2021). Short term memory deficits, examined via the 4-item recall, were observed in 32% of participants who completed the assessment, including individuals with a positive (30%) or negative (34%) SARS-CoV-2 test (Graham et al., 2021). In addition, attention deficits, examined via the serial 7s task, were observed in 27% of participants who completed the assessment, including individuals with a positive (24%) or negative (30%) SARS-CoV-2 test (Graham et al., 2021). Overall, individuals with positive versus negative SARS-CoV-2 tests did not score significantly different on cognitive assessment. However, a mild to moderate cognitive impairment was evident in both participant groups (Graham et al., 2021). Individuals who tested positive for SARS-CoV-2 scored significantly worse than the normative population on measures of attention and working memory (Graham et al., 2021). Interestingly, there was no relationship

between participant report of recovery to premorbid function and performance on cognitive assessment tasks. Despite these findings from Graham et al., this sample likely does not represent the general population of non-hospitalized COVID-19 as individuals were recruited from a Neuro-Covid-19 clinic in Chicago and inclusion criteria included participants experienced neurologic symptoms for a minimum of 6 weeks (Graham et al., 2021).

Bungenberg et al. (2021) conducted a cross-sectional study assessing long-term subjective symptoms in individuals with COVID-19 and findings were compared between hospitalized ($n = 21$) and non-hospitalized ($n = 29$) individuals (Bungenberg et al., 2021). Of note, all participants had long-term symptoms lasting a minimum of 4 weeks (Bungenberg et al., 2021). Multiple measures of cognitive function were provided, including: MoCA, Test of Attentional Performance, and a Stroop test. Changes in taste and/or smell (74%) and fatigue (66%) were frequently reported in the acute phase, while the cognitive complaints (70%) were commonly reported outside of the acute phase (Bungenberg et al., 2021). Cognitive complaints were reported regardless of hospitalization status. For example, 69% of non-hospitalized participants and 38% of hospitalized participants reported attention impairments (Bungenberg et al., 2021). In addition, 31% of non-hospitalized participants and 48% of hospitalized participants reported memory deficits (Bungenberg et al., 2021). Regarding objective cognitive function, “Overall, neuropsychological performance was within standard normative references, according to age and/or education published norms, with PR values above 16. Independently of hospitalization status, there was a tendency for worse performance in attention, psychomotor speed and memory task” (Bungenberg et al., 2021, p. 146-147).

The above findings support an array of neurocognitive consequences in individuals with COVID-19 despite hospitalization status or phase of disease progression. In summary, attention

and memory deficits were frequently documented in individuals with COVID-19. The WHO even includes “memory, concentration or sleep problems” in a list of most frequent symptoms associated with post COVID-19 condition (2021b). Given the acute and persistent cognitive consequences associated with COVID-19, it is likely that COVID-19 may also have an impact on QOL.

The Impact of COVID-19 on Quality of Life (QOL)

The COVID-19 pandemic has had widespread impacts around the world. While COVID-19 cases in the US were first reported in January 2020, cases climbed dramatically in the US by the middle of March 2020 (Schuchat, 2020). Travel restrictions began in February 2020, followed by recommendations to reduce travel and attendance at large gatherings by the middle of March (Schuchat, 2020). Stay-at-home orders were put into effect, in-person instruction at schools ceased, and nonessential businesses were closed (Schuchat, 2020). While these changes impacted individuals differently, students and many non-essential workers began working from home, social distancing guidelines limited social activities, and many individuals became unemployed. Therefore, regardless of an individual being diagnosed with COVID-19 or not, one could argue that the COVID-19 pandemic may impact an individuals’ QOL, particularly in social domain. However, QOL may also be affected as a direct result of acute and/or long-term cognitive consequences following diagnosis of COVID-19.

As previously discussed, research findings suggest that individuals are at risk for acute and persistent cognitive consequences due to COVID-19. The potential acute and long term affects from COVID-19 may impact an individual’s ability to carry out activities of daily living, such as managing finances or returning to work. According to the WHO (2021b), “People with post COVID-19 condition, also known as “long COVID”, may have difficulty functioning in

everyday life. Their condition may affect their ability to perform daily activities such as work or household chores.” Changes in QOL are not unexpected and may vary given the cognitive areas at risk for impairment following COVID-19. For example, individuals with COVID-19 may experience different social QOL, emotional QOL, or cognitive QOL. In addition, deficits in specific cognitive areas may result in specific functional consequences impacting certain domains of QOL.

One may suspect reduced QOL at the onset of illness. However, reduced QOL in individuals with COVID-19 persists outside the acute phase of COVID-19. QOL has been studied in previously hospitalized individuals with moderate to severe COVID-19 who were two to three months post onset of COVID-19 (Raman et al., 2021). When compared to controls, individuals with COVID-19 reported significantly higher symptom scores pertaining to depression and significantly lower QOL in all areas assessed, including in *role limitation due to emotional health*, *emotional well-being*, and *general health* (Raman et al., 2021). While Raman et al. utilized controls for comparison, Carfi et al. (2020) determined QOL in individuals with COVID-19 who were previously hospitalized using the EuroQOL visual analog scale at the time of data collection (on average participants were 60 days since symptom onset), as well as prior to the individuals’ COVID-19 diagnosis. Forty-four percent of individuals had reduced QOL (Carfi et al., 2020). Michelen et al. (2021) utilized different procedures and conducted a living systematic review which included studies with hospitalized and/or non-hospitalized individuals a minimum of 12 weeks following onset of COVID-19. Based on studies from either a mixed setting ($n = 2$) or hospitalized setting ($n = 1$), meta-analysis also revealed reports of lower quality of life in 37% of participants (Michelen et al., 2021).

Poudel et al. (2021) conducted a rapid review of studies looking at the effect of COVID-19 on health-related quality of life following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (as cited from Moher et al., 2009). The main inclusion criteria included the following: participants were symptomatic, either had suspected or diagnosed COVID-19 via a lab test, and the COVID-19 severity varied (Poudel et al., 2021). For purposes of this review, long covid was defined as “>4 weeks from onset of symptoms” while acute covid was defined as “≤4 weeks from onset of symptoms” (p. 4). Twelve studies were included in the review (Poudel et al., 2021). Of these studies, 11 included individuals meeting Poudel et al.’s definition of long covid. However, only one study was conducted on long covid patients more than 12 weeks after the onset of COVID-19 symptoms (Poudel et al., 2021). In addition, only two of these studies were conducted on non-hospitalized individuals, and one study was conducted with both non-hospitalized and hospitalized individuals (Poudel et al., 2021). Of the two studies conducted on non-hospitalized individuals, one was conducted in Vietnam and reported health related QOL approximately two weeks following COVID-19 symptom onset (Poudel et al., 2021 as cited from Nguyen et al., 2020), while the second study was conducted in Belgium and reported health related QOL approximately ten to 12 weeks following COVID-19 symptom onset (Poudel et al., 2021 as cited from Meys et al., 2020). The study including hospitalized and non-hospitalized individuals was conducted in the Netherlands and reported health related QOL approximately 13 weeks following symptom onset (Poudel et al., 2021 as cited from van den Borst et al., 2020). However, the sample of non-hospitalized individuals had persistent symptoms for over six weeks, and participants either had a positive COVID test or suspected SARS-CoV-2 based on clinical presentation (van den Borst et al., 2020). Van den Borst et al. (2020) conducted a prospective observational study which utilized a standardized

health assessment. This included, among other tasks, a cognitive impairment screener: Telephone Interview of Cognitive Status, a measure of subjective cognitive function: Cognitive Failure Questionnaire, and measures of health status: 1. the Short Form Health survey (SF-36), and 2. Nijmegen Clinical Screening Instrument (NCSI) (van den Borst et al., 2020). The NCSI examines quality of life (van den Borst et al., 2020). Findings revealed, “Across all NCSI health status domains, substantial proportions of patients reported severe problems. This was most pronounced in the domains fatigue (69%), functional impairments in daily life (64%), and general quality of life (72%)” (van den Borst et al., 2020, p. e1094). When comparing SF-36 and NCSI scores across individuals with varying levels of COVID-19 severity, “patients with mild disease reported significantly worse health status on most subscales of the SF-36 and on the subdomains of the NCSI as compared with discharged patients with moderate-to-critical disease” (van den Borst et al., 2020, p. e1094). Despite these findings, van den Borst et al. address limitations which could have impacted findings, such as the criteria that individuals referred with mild COVID had persistent symptoms for over 6 weeks.

Similar to Poudel et al. (2021), Malik et al. (2022) also followed PRISMA guidelines to conduct a systematic review. More specifically, Malik et al. (2022) conducted a meta-analysis on the poor quality of life prevalence following COVID-19 and a meta-regression on “the effects of persistent symptoms and ICU admission on the poor quality of life” (p. 254). Twelve studies ($n = 4,828$ post-acute COVID-19 syndrome patients) were included, with most studies reporting findings from hospitalized individuals (Malik et al., 2022). Data collection occurred between 30- and 180-days following hospital discharge (Malik et al., 2022). Poor QOL was reported in 58% of patients (Malik et al., 2022). Upon further analysis, “the pooled prevalence of individual factors in EQ-5D-5L questionnaire estimating poor quality of life was mobility (36%, 95% CI:

10%-67%), personal care (8%, 95% CI: 1%-21%), usual quality (28%, 95% CI: 2%-65%), pain/discomfort (42%, 95% CI: 28%-55%), anxiety/depression (38%, 95% CI: 19%-58%)” (Malik et al., 2022, p. 257).

Albu et al. (2021) conducted a cross-sectional observational study aimed to determine consequences following COVID-19 and functional impact of these consequences (p. 470). Participants were adults with a COVID test (PCR or serology) who had long term symptoms or COVID sequelae ($n = 30$) (Albu et al., 2021). Of note, one exclusion criterion was that participants had “persistent symptoms of confirmed COVID-19 without indications for rehabilitation interventions (e.g., anosmia, dysgeusia, pain symptoms)” (Albu et al., 2021, p. 470). With regard to cognitive function, consistent with the literature previously reported, “12 of 14 patients reporting subjective cognitive complains (e.g., difficulties with focusing attention, concentration and short memory problems) and 13 of 15 patients without cognitive complains scored lower than expected by age and education in at least one cognitive test. However, reporting subjective cognitive complains was unrelated to altered cognitive tests” (p. 472). Findings indicated post-ICU and non-ICU participants scored similarly on functional independence measures, cognitive-affective state and quality of life (Albu et al., 2021). There was a relationship between impact of physical fatigue, cognitive fatigue, and social fatigue, with reduced quality of physical and social life, in addition to increased depression (Albu et al., 2021). Impact of social fatigue also had a significant negative relationship with psychological quality of life (Albu et al., 2021). A significant relationship was found between increased anxiety and depression and lower quality of life (physical, psychological, and social) (Albu et al., 2021). The authors proceed by adding, “at the cohort level, patients presenting with depression were more

likely to have altered attention and verbal recognition functions” (Albu et al., 2021, p. 478). These findings highlight multiple variables which may relate to QOL following COVID-19.

In addition to investigating neurological manifestations, Graham et al. (2021) also examined QOL in the areas of cognition and fatigue in non-hospitalized COVID-19 long haulers. Individuals with positive ($n = 50$) versus negative ($n = 50$) SARS-CoV-2 tests did not score significantly different on QOL measures (Graham et al., 2021). However, a moderate impairment in cognition and fatigue QOL was discovered in both participant groups (Graham et al., 2021). All participants (individuals who tested positive and negative for SARS-CoV-2) scored significantly worse than the normative population for QOL in the domains of cognition and fatigue (Graham et al., 2021). Further analysis was calculated using QOL scores and cognitive task scores. Interestingly, QOL scores pertaining to fatigue were moderately related to the following: processing speed, executive function, and working memory (Graham et al., 2021). In addition, QOL scores pertaining to cognition and working memory were correlated (Graham et al., 2021). Lastly, participant report of how they feel recovery is going based on premorbid function had a moderate relationship with QOL in the domains of both cognition and fatigue (Graham et al., 2021).

Ceban et al. (2022) conducted a systematic review and meta-analysis to determine the proportion of individuals at least 12 weeks post COVID experiencing cognitive impairment and fatigue. Additional objectives included determining the functional consequences secondary to post-COVID-19 syndrome (Ceban et al., 2022). Hospitalization status was determined based on at least 80% of participants in the study being hospitalized (Ceban et al., 2022). This review included 81 studies; however, 43 studies were included for quantitative analysis determining the impact of COVID-19 on cognition (Ceban et al., 2022). Findings revealed cognitive impairment

in 22% of participants in the chronic phase following COVID-19 (at least 12 weeks post COVID-19) ($n = 13,232$) (Ceban et al., 2022). With regard to cognitive impairment, hospitalization status did not result in statistically significant differences (Ceban et al., 2022). Surprisingly, “there was no significant difference in the proportions reporting cognitive impairment at <6 and ≥ 6 months follow-up” (Ceban et al., 2022, p. 126). Of studies reporting functional outcomes, functional impairment was documented in 21-63% of participants, while activity impairment varied more across studies (1-68%). Activity impairment included things such as challenges with activities of daily living (Ceban et al., 2022). Ceban even highlighted, “All studies investigating functional outcomes reported marked functional impairment in a sample subset” (Ceban, 2022, p. 126).

Bungenberg et al. (2021) conducted a cross-sectional study with hospitalized ($n = 21$) and non-hospitalized ($n = 29$) individuals following COVID-19 (Bungenberg et al., 2021). Hospitalization status was based on hospitalization during the acute phase of COVID-19 (Bungenberg et al., 2021). Inclusion criteria included symptoms lasting a minimum of four weeks (Bungenberg et al., 2021). Fatigue severity was significantly related to lower QOL as measured via the EQ5D. Lower performance on measures of psychomotor speed and attention were also related to lower scores on the EQSD (a health status measure for quality of life), as well as excessive daytime sleepiness (Bungenberg et al., 2021). When comparing participants based on hospitalization status, “PROMs identified fatigue, reduced sleep quality, and increased anxiety and depression in both groups but more pronounced in non- hospitalized patients” (Bungenberg et al., 2021, p. 141)

Tabacof et al. (2022) conducted a cross-sectional observational study on post-acute COVID-19 syndrome and the functional impact from COVID-19 symptoms. Despite 89% of

participants being non-hospitalized, all participants had a post-acute COVID-19 syndrome diagnosis (symptoms lasting more than 12 weeks from onset) (Tabacof et al., 2022). Participants ($n = 156$), who were recruited from a post-acute COVID-19 clinic, were a median of 351 days post-infection (Tabacof et al., 2022). Multiple survey instruments were administered, including the Neuro-Qol to screen for cognitive function and the EuroQol: 5 dimension, 5 level (EQ-5D-5L) to screen for health-related quality of life. Fatigue (82%), brain fog (67%), headache (60%), sleep disturbance (59%), and dizziness (54%) were found to be the most frequently reported symptoms (Tabacof et al., 2022). Interestingly, one measure found problematic fatigue in 78% of participants. Poor cognitive function was noted, with 63% of participants scoring “for at least mild cognitive impairment on the Neuro-Qol” (Tabacof et al., 2022, p. 50). Based on the health related QOL measure, domains most frequently affected included: self-care, anxiety/depression, and usual activities (Tabacof et al., 2022). Tabacof et al. (2022) highlight the importance of these findings: “The presence of cognitive dysfunction in more than half (63%) of patients, in combination with reduced usual activities and self-care scores on the EQ-5D-5L, highlights that patients with PACS may have a reduced ability to participate in society” (p. 51).

Davis et al. (2021) highlight the functional impact of cognitive dysfunction and/or memory impairments, as they found 86% of participants who were employed reported a mild to severe inability to work. Many individuals with cognitive dysfunction and memory impairment also report being mild to severely unable to: make serious decisions (approximately 75%), communicate their thoughts (approximately 68%), converse with others (approximately 62%), drive (approximately 54%), remember medication (approximately 53%), follow simple instructions (approximately 51%), watch children (approximately 45%), cook or use hot items (approximately 42%), shower or bath regularly (approximately 28%), remember the year or

month (approximately 26%), feed themselves (approximately 20%), or return home without getting lost (approximately 10%) (Davis et al., 2021). The impact from COVID-19 may even affect one's ability to return to work. For example, when comparing work schedules prior to COVID-19 onset, 45% needed a reduction in work schedule (Davis et al., 2021). In addition, many participants (22%) reported they were not currently working due to COVID-19. These findings are particularly concerning as most participants included in the study were non-hospitalized (Davis et al., 2021).

While Davis et al. (2021) primarily included non-hospitalized individuals, their study also included individuals who were hospitalized (8%) or who sought care in an urgent care or emergency room without hospitalization (35%). However, Vaes et al. (2020) reported findings on care dependency exclusively from non-hospitalized individuals ($n = 1837$) on average 79 days post COVID-19 symptoms onset. Despite this study being on non-hospitalized individuals, recruitment included COVID-19 Facebook groups for individuals with long-standing complaints (Vaes et al., 2020). Seventeen percent had a confirmed COVID-19 diagnosis, 45% were suspected to have COVID-19 based on medical diagnosis given symptoms, and 38% “were undiagnosed at the start of the presumed infection” (Vaes et al., 2020, p. 3). While good health prior to COVID-19 was reported in 86% of participants, good health was only reported by 6% of participants after COVID-19. One surprising finding was 98% of participants reported fatigue following COVID-19. Findings revealed a significant increase in care needs when comparing care needs post COVID-19 to care needs prior to illness (Vaes et al., 2020). Despite being non-hospitalized individuals, based on the Care Dependency Scale, 31% were care-dependent (Vaes et al., 2020). These findings highlight the functional impact following COVID-19, even in non-hospitalized individuals.

Johnsen et al. (2021) conducted a cross sectional study on hospitalized ($n = 34$) and non-hospitalized (23) individuals with COVID-19. Study participation occurred either 3 months following hospital discharge or after acute disease (for non-hospitalized individuals) (Johnsen et al., 2021). Non-hospitalized individuals were referred due to their symptoms (Johnsen et al., 2021). While this study assessed pulmonary function, it also assessed quality of life and cognitive function. Eighty-nine percent of participants perceived large cognitive difficulties (Johnsen et al., 2021). However, the percent of individuals with documented cognitive impairments varied between hospitalized (59-66%) and non-hospitalized (31-44%) individuals. The range in percentiles is due to the possible cut off scores (Johnsen et al., 2021). There was no significant difference between QOL scores measured via the 5 Dimension 5 Level Quality of Life Questionnaire (EQ-5D-5L) when comparing scores from hospitalized and non-hospitalized individuals (Johnsen et al., 2021). However, findings revealed a significant correlation between QOL scores measured via the EQ5D-5 index and subjective cognitive status, as well as the EQ5D-5 index and post-covid performance status measured via the Post-COVID-19 Functional Status Scale (Johnsen et al., 2021). Based on the Work Productivity and Activity Impairment Questionnaire: General Health and Disease Specific Version, the percent overall work impairment due to health and percent activity impairment due to health were significantly higher in non-hospitalized individuals (Johnsen et al., 2021). There also appeared to be a correlation between cognitive function measured via the Screen for Cognitive Impairment in Psychiatry Danish Version and quality of life measured via the EQ5D Index (Johnsen et al., 2021, figure 4). Johnsen et al. (2021) found, despite hospitalization, cognitive impairment and reduced quality of life may occur.

The above findings highlight functional impairment and reduced QOL in individuals with COVID-19. In addition, relationships have been documented between different measures of QOL and cognitive functioning (Graham et al., 2021; Johnsen et al., 2021). However, additional research is warranted to better understand the relationship between QOL and cognitive functioning in individuals following COVID-19.

The Impact of Premorbid Verbal IQ on Cognitive Performance and QOL

Verbal IQ is “a measure of acquired knowledge, verbal reasoning, and attention to verbal materials” (Lang, 2011), while premorbid intelligence is defined as “an estimate of a person’s intellectual functioning prior to known or suspected onset of brain disease or dysfunction” (Schoenberg et al., 2011). Verbal intellectual abilities may be determined using instruments such as the Lexical Orthographic Familiarity Test (LOFT) or the Wechsler Test of Adult Reading (WTAR) (Leritz et al., 2008). Some investigators have used verbal intelligence instruments as a gross measure of premorbid intellectual functioning.

Premorbid intelligence has been estimated via performance on the WTAR and used as a proxy for cognitive reserve (Steward et al., 2018). Of note, the WTAR measures premorbid intelligence (Venegas et al., 2011) using a verbal task. Steward et al. studied individuals with traumatic brain injury (TBI) and controls using the WTAR and measures of cognitive performance such as the Trail Making Test Part A and B, and the California Verbal Learning Test- second edition (Steward et al., 2018). Findings revealed greater cognitive reserve, or premorbid IQ, was related to greater cognitive function in the processing speed/executive function, memory, and verbal fluency domains (Steward et al., 2018).

Similar to Steward et al., Fraser et al. (2019) assessed premorbid IQ and cognitive performance in individuals with TBI and non-brain injured participants. The National Adult

Reading Test was used as a measure of premorbid IQ and the scores were used to determine the Full Scale Intelligence Quotient from the Wechsler Adult Intelligence Scale-III (Fraser et al., 2019). Of note, this measure was completed following considerable cognitive recovery, approximately two to five years after injury (Fraser et al., 2019). Results revealed higher-premorbid IQ, shorter post traumatic amnesia duration, and younger age were significant predictors of superior cognitive function on measures of attention, memory, and executive functioning approximately 44 days following injury (Fraser et al., 2019). There was also a relationship between higher premorbid IQ and greater cognitive recovery measured on average 3.7 years after injury when initial cognitive performance was controlled for (Fraser et al., 2019).

While the studies above were conducted in individuals with TBI, similar procedures have been conducted in individuals with multiple sclerosis (MS). For example, Sumowski et al. (2009) administered the Wide Range Achievement Test- Third Edition: Reading subtest, an estimate of premorbid verbal intelligence, as a proxy for cognitive reserve to individuals with MS and control participants (Sumowski et al., 2009). In addition, participants also completed measures of cognitive performance such as the Symbol Digit Modalities Test- Oral Version, Two Trial version of the Paced Auditory Serial Addition Test (PASAT), and the Logical Memory subtests from the Wechsler Memory Scale-Revised (Sumowski et al., 2009). While there was not a significant relationship between simple processing efficiency and cognitive reserve, there was a large significant relationship between the PASAT (complex information processing efficiency) and cognitive reserve in individuals with MS (Sumowski et al., 2009). Similarly, a large significant relationship was reported between cognitive reserve and verbal learning, as well as verbal memory, in individuals with MS (Sumowski et al., 2009).

Sumowski argues cognitive reserve moderates cognitive performance, as increased cognitive reserve appears to protect against information processing inefficiency, verbal learning impairments, and verbal memory impairments in individuals with MS (Sumowski et al., 2009).

Benedict et al. (2010) used education and outcomes from the North American Adult Reading Test (NAART), an estimated premorbid IQ measure, as a proxy for cognitive reserve in individuals with MS. Two measures, the Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Additional Test (PASAT), were used to determine an information processing efficiency index (Benedict et al., 2010). Benedict et al., (2010) report, “Our primary finding was that [cognitive reserve] measures moderated the degree of decline on [neuropsychological] tests assessing [information processing] efficiency. Patients with low reserve were likely to show decline over time, especially on the [Symbol Digit Modalities Test], whereas those with high [cognitive reserve] did not.” (p. 832). However, none of the relationships between the measures of cognitive reserve and the baseline SDMT, baseline PASAT, or the baseline information processing index were statistically significant (Benedict et al., 2010). These studies highlight relationships between premorbid IQ and cognitive performance. However, to our knowledge, the relationship between premorbid Verbal IQ and cognitive performance has not been studied in non-hospitalized individuals with COVID-19.

Determining the relationship between premorbid Verbal IQ, previously used as a measure of cognitive reserve, and cognitive function is important as cognitive reserve may impact QOL. For example, Lara et al. (2017) utilized a nationally representative sample of the non-institutionalized adult Spanish population ages 50 and older ($n = 1973$) to determine the relationship between cognitive reserve and QOL, and the role additional factors play in this relationship. Participants completed the Cognitive Reserve Questionnaire, WHOQOL-AGE,

cognitive tasks, and additional measures (Lara et al., 2017). Of note, the cognitive tasks included measures of learning and short-term memory, attention and working memory, and verbal fluency (Lara et al., 2017). Findings revealed a significant relationship between higher cognitive reserve and increased QOL (Lara et al., 2017). Additional analysis revealed larger mediating effects from disability, and smaller mediating effects from cognitive function and depression (Lara et al., 2017).

Verbal intelligence has been associated with factors outside of QOL which may indirectly influence QOL. For example, Nikolaev et al. (2016) found verbal intelligence has a small positive significant relationship with happiness based on data from on a nationally representative survey of Americans. This relationship also persists when controlling for additional variables such as family income (Nikolaev et al., 2016). Although this is not a study on QOL, one might expect increased happiness to be associated with QOL.

Despite these findings pertaining to QOL, it should be noted that investigators have also documented no relationship between intelligence and technical ability with QOL in individuals enrolling in a military department (Watten et al., 1995). Research is warranted to determine the relationship between premorbid verbal intelligence and cognitive performance, as well as the relationship between premorbid verbal intelligence and QOL in individuals following COVID-19.

Purpose of the Present Study

While research has shifted to include non-hospitalized individuals post COVID-19 onset, most studies appear to have a bias sample of non-hospitalized individuals which may not truly represent non-hospitalized individuals in the general public. As the list of cognitive sequela following COVID-19 is growing, this is particularly concerning as non-hospitalized individuals

likely account for a large proportion of individuals with COVID-19. Given the high prevalence of COVID-19 paired with literature documenting cognitive consequences secondary to COVID-19 in addition to reduced QOL and functional impairment, additional research is urgently warranted to determine the long-term impact of COVID-19 on cognition and QOL in non-hospitalized individuals in the chronic phase following COVID-19 with recruitment from the general public. Determining the long-term consequences associated with COVID-19 and their impact on QOL is critical as it may inform assessment and treatment of cognitive impairment following COVID-19. In addition, determining the relationship between premorbid Verbal IQ with cognitive performance and QOL is necessary to provide a more comprehensive understanding of cognition and QOL following COVID-19. Therefore, the present study will aim to determine the relationship between the following: (a) cognitive performance and QOL, (b) premorbid Verbal IQ and QOL, (c) cognitive performance and premorbid Verbal IQ, and (d) length of time since COVID-19 diagnosis and QOL. In addition, this study will aim to determine if cognitive performance and premorbid Verbal IQ predict QOL measured via different domains in individuals at least 12 weeks post COVID-19 diagnosis who were not hospitalized due to COVID-19.

It was hypothesized there would be a strong positive relationship between cognitive performance, as measured by the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) Two-Factor score (Memory Composite and Speed Composite), and QOL in both cognitive and emotional domains, as determined by the Neuro-QOL Cognitive Function and Neuro-QOL Positive Affect and Well-Being measure outcomes. This hypothesis was based on the idea that cognitive impairment may result in functional impairments which in turn may impact QOL. For example, recent literature suggests potential for persistent cognitive sequela in

non-hospitalized individuals following COVID-19 (Ceban et al., 2022; Graham et al., 2021). As previously highlighted by Ceban et al.'s systematic review and meta-analysis (2022), of studies reporting functional outcomes, functional impairment was documented in 21-63% of participants and activity impairment varied across studies (1-68%). Furthermore, reduced QOL has been reported in non-hospitalized individuals outside of the acute phase of disease progression (Graham et al., 2021; Tabacof et al., 2022). Based on literature documenting a significant relationship between higher cognitive reserve and increased QOL (Lara et al., 2017), it was expected that there would be a positive relationship between premorbid Verbal IQ, as measured by the LOFT raw score, and QOL in both domains assessed. It was also expected that there would be a positive relationship between cognitive performance and premorbid Verbal IQ. This prediction was supported by literature documenting relationships between higher premorbid IQ measured using verbal tasks and better cognitive performance (Steward et al., 2018). While one may expect fluctuations in QOL in the acute phase following COVID-19, this study assessed individuals at least 12 weeks after COVID-19 diagnosis. Therefore, no relationship was expected between QOL in both domains assessed and time since COVID-19 diagnosis. It is critical to acknowledge the challenge associated with predicting a null result given the small sample size, which is discussed in detail below. Lastly, it was expected that cognitive performance, as measured by the ImPACT Two-Factor score (Memory Composite and Speed Composite), and premorbid Verbal IQ, as measured by the LOFT raw score, predict both measures of QOL.

CHAPTER III: METHODS

Participants

Participants were recruited through use of flyers posted at the University of North Carolina Greensboro, emails to students and/or faculty at multiple universities, posting flyers on Facebook groups for individuals with COVID-19, posting flyers on the American Speech-Language Hearing Association-Neurogenic Communication Disorders Special Interest Group discussion board, word of mouth, and snowball sampling.

Extensive inclusion and exclusion criteria were utilized in attempts to control for comorbidities which could confound results. Inclusion criteria included the following: between the ages of 18-59, tested positive for COVID-19, at least 12 weeks after COVID-19 diagnosis, primary language is English, resides in the United States, completed high school, never hospitalized or sought care in an emergency department due to COVID-19 or COVID-19 related symptoms, no history of brain injury (including no history of concussion), no history of stroke, no history of seizures, not currently taking medication for anxiety or depression, no significant history of treatment for anxiety or depression or post-traumatic stress disorders (PTSD), no history of attention deficit disorders (ADD) or attention deficit hyperactive disorder (ADHD), no perceived cognitive deficits *prior* to COVID-19 diagnosis (ex. difficulty with memory, difficulty with attention), not previously evaluated for cognitive impairment or dementia, no history of a learning disability, adequate hearing per self-report, adequate vision per self-report, access to a desktop computer or laptop (device must have a color monitor, mouse or track pad pointing device, working video camera and microphone/speaker, and access to a web browser), and access to reliable internet.

Exclusion criteria included the following: younger than 18 years of age or older than 59 years of age, did not test positive for COVID-19, COVID-19 diagnosis was obtained less than 12 weeks from the time of data collection, primary language is not English, resides outside of the United States, did not complete high school, hospitalized due to COVID-19 or COVID-19 related symptoms, history of brain injury (including concussion), history of stroke, history of seizures, currently taking medication for anxiety or depression, significant history of treatment for anxiety or depression or PTSD, history of ADD or ADHD, perceived cognitive deficits *prior* to COVID-19 diagnosis, previously evaluated for cognitive impairment or dementia, history of a learning disability, current self-reported hearing difficulties, current self-reported trouble with vision, no access to a desktop computer or laptop (or device does not have a color monitor, mouse or track pad pointing device, working video camera and microphone/speaker, and access to a web browser), and no access to reliable internet.

Twenty-three participants met the inclusionary/exclusionary criteria and completed the study protocol. Refer to table 2 for participant demographic information.

Table 2. Participant Demographics

Participant	Age	Education	Gender	Days post COVID-19 diagnosis
1	23	16	Female	346
2	25	17	Female	463
3	51	13	Female	271
4	36	16	Male	307
5	35	14	Male	321
6	37	18	Female	246
7	41	17	Female	251
8	26	17	Female	274
9	36	16	Female	98
10	50	14	Female	448

11	59	16	Female	348
12	59	22	Female	110
13	58	16	Female	97
14	50	16	Female	370
15	43	14	Female	137
16	38	16	Female	409
17	52	15	Female	167
18	33	18	Female	475
19	31	18	Female	141
20	34	16	Female	126
21	36	13	Female	377
22	43	17	Female	425
23	43	18	Female	212
Averages	41	16	F=21; M=2	279

Note. If participants reported <12 years of education, it was assumed they were listing secondary education since inclusion criteria included “completed high school”. Therefore, 12 years were added to the education reported. Unique scenarios for determining days post COVID-19 diagnosis are discussed below.

All participants self-reported being tested for COVID-19 via nasal swab. Nineteen participants reported being vaccinated (Pfizer= 12; Johnson & Johnson (Janssen)= 2; Moderna= 5) while 4 reported being unvaccinated. A list of comorbidities was provided on the intake form. With regard to responses pertaining to the list of comorbidities included on the intake form, 18 participants denied being diagnosed with any of the comorbidities listed. However, two participants endorsed hypertension, two endorsed asthma, and two endorsed obesity (one participant endorsed both hypertension and obesity).

Instruments

Participant Intake Form

An electronic participant intake form was used to obtain general participant information, health information pertaining to COVID-19, and subjective symptoms due to COVID-19. General participant information collected included information such as age, gender, years of education, and comorbidities (select all that apply from a list including: chronic obstructive pulmonary disease, asthma, cardiac disease, hypertension, diabetes mellitus, and obesity). In addition, individuals reported the date they received a positive COVID-19 diagnosis from a healthcare provider, selected how they were tested for COVID-19 (ex. nasal swab versus blood test), reported if they had received the COVID-19 vaccine and if so, which vaccine they received. Participants were asked three questions regarding current symptoms due to COVID-19. The three questions included neurological manifestations grouped based on the three categories used by Mao et al. (2020): central nervous system manifestations, peripheral nervous system manifestations, and skeletal muscular injury manifestations. However, modifications were made to the symptoms listed in each category of neurological manifestations. All neurological manifestation questions followed the same question format: *Are you experiencing any of the following new or worsening symptoms since testing positive for COVID-19?* This question was followed by a list of symptoms grouped based on either central nervous system manifestations (severe dizziness, severe headaches/migraines, impaired consciousness (confusion or delirium), ataxia, dizziness or vertigo, taste impairment, smell impairment, vision impairment, fatigue), peripheral nervous system manifestations (shooting/burning pain into a limb, tingling sensations, numbness, burning sensations), or skeletal muscular injury manifestations (skeletal muscle pain, joint pain, weakness).

Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

The ImPACT Version 4 (ImPACT Applications Inc., 2021b) was utilized as a measure of objective cognitive function. The ImPACT is an electronic neurocognitive measure traditionally used for management of concussion (ImPACT Applications Inc., 2021a). This specific instrument was selected due to the sensitivity and specificity (ImPACT Applications Inc., 2021a as cited from Schatz & Pardini et al., 2006), as well as validity (ImPACT Applications Inc., 2021a as cited from Maerlender et al., 2010 and Schatz & Putz, 2006). In addition, the ImPACT is an electronic measure aiding in ease of administration via telepractice.

The ImPACT is normed for use with individuals aged 12 to 80. This instrument takes approximately 20 minutes to complete and is used to assess the following: Sequencing/Attention, Word Memory, Visual Memory, and Reaction Time (ImPACT Application Inc., 2021a). The ImPACT includes questions pertaining to demographic information, a Post Concussion Symptoms Inventory, and 6 modules: Word Memory (including a delayed condition), Design Memory (including a delayed condition), X's and O's, Symbol Match, Color Match, and Three Letters (ImPACT Applications Inc., 2021a). Each of the modules evaluate specific cognitive areas. For example, the Word Memory module assesses verbal recognition memory as well as attentional processes while the X's and O's module assesses visual processing/motor speed as well as visual working memory (ImPACT Applications Inc., 2021a).

Scoring is generated electronically and reported via a clinical report. While there are multiple different scores derived from the ImPACT, the Two-Factor Score was utilized for analysis due to literature documenting relationships between the four Core Composite scores (Maerlender et al., 2013), literature supporting the Two-Factor score (Gerrard et al., 2017), and literature validating the Two-Factor score for the ImPACT (ImPACT Applications Inc., as cited

from Schatz & Maerlender, 2013). The Two-Factor Score yields two composites, the Memory Composite and Speed Composite, based on the four Core Composites. The four Core Composite score areas include the: Verbal Memory Composite, Visual Memory Composite, Visual Motor Speed Composite, and Reaction Time. According to the ImPACT Applications, Inc. manual (2021a), “The Composite Scores provide a summary score that represents unweighted average raw scores for the component subtests. Scores are expressed as percentiles for each input device (computer mouse and trackpad) separately relative to individuals of their own age group and sex” (p. 14). The Memory Composite is determined based the Verbal Memory and Visual Memory Core Composite scores. The Speed Composite is determined based on the Motor Speed and Reaction Time Core Composite scores. According to the ImPACT Applications, Inc. manual (2021a), “The Two-Factor Scores are calculated as Z-scores (subtracting the user’s score from the group mean and dividing by the standard deviation: $(X-\text{Mean})/SD$) and are presented as percentile ranks. ... the Speed Composite is calculated by subtracting the Motor Speed and Reaction Time Z-scores and dividing by 2... The Memory Composite is calculated by summing the Verbal Memory and Visual Memory Z-scores, and dividing by 2” (p. 17). It is important to note that the Two Factor Score is controlled for both age and gender (ImPACT Applications Inc., 2021a). Given the Two-Factor Scores are calculated as Z-scores, higher scores indicate better performance for both the Speed and Memory Composites.

Lexical Orthographic Familiarity Test (LOFT)

The LOFT was selected to serve as a measure of premorbid Verbal IQ as this instrument “indexes preserved lexical information to estimate premorbid intelligence” (Leritz et al., 2006). In addition, the LOFT was selected due to its reliability, internal consistency, and validity (Leritz et al., 2008). This instrument is comprised of 50 forced choice items to determine lexical

familiarity (Leritz et al., 2008). Each question includes a pair of words: one word from the Wechsler Test of Adult Reading and one archaic English word (Leritz et al., 2008). Respondents are prompted to complete the following: “Please underline the one word that looks the most familiar to you. If you know both of the words then choose the one that is the most familiar” (Leritz et al., 2008, p. 6). Scoring yields a raw score based on the number of items the respondent answers correctly (Leritz et al., 2008). Therefore, higher scores indicate better performance.

Although the LOFT is not an electronic measure, this instrument can be administered remotely with minimal modification to the original instrument. Unlike other measures of crystallized verbally mediated IQ, the LOFT does not rely on respondent’s verbal output (i.e., word reading), which is subject to variables that could confound results when using remote administration (i.e., poor audio). The LOFT was administered electronically using the same 50 items as paper administration. Modification of the instructions will include prompting the individual to *select* their response instead of *underlining* their response.

Of note, while the LOFT has been validated to determine Verbal IQ in individuals with aphasia and non-brain damaged individuals, investigators have noted that the LOFT could reflect premorbid and/or current intelligence (Leritz et al., 2008). However, the LOFT appeared to be a superior measure of premorbid abilities in individuals with aphasia when compared to the Wechsler Test of Adult Reading (Leritz et al., 2008). In addition, Leritz et al. reported a significant relationship between LOFT scores and education. Therefore, the LOFT was selected as a measure of premorbid Verbal IQ.

Quality of Life Measures: Cognitive Function and Positive Affect and Well-Being

Two separate QOL in Neurological Disorders measures were selected for administration. The two measures included: 1. Neuro-QOL Item Bank v1.0- Positive Affect and Well-Being

(Gershon et al., 2012), and 2. Neuro-QOL Item Bank v2.0- Cognitive Function (Gershon et al., 2012). These measures assess different domains of health related QOL in adults with neurological disorders (NINDS, 2015). For example, the Positive Affect and Well-Being QOL instrument is a measure of emotional health, while the Cognitive Function QOL instrument is a measure of cognitive health (NINDS, 2015). The NINDS User Manual (2015) defines the Cognitive Function domain as: “Perceived difficulties in cognitive abilities (e.g., memory, attention, and decision making, or in the application of such abilities to everyday tasks (e.g., planning, organizing, calculating, remembering and learning)” (p. 6), and Positive Affect and Well-Being domain as: “Aspects of a person’s life that relate to a sense of well-being, life satisfaction or an overall sense of purpose and meaning” (p. 6).

These Neuro-QOL measures were selected for administration due to being validated measures (NINDS, 2015) which can be administered electronically. Both measures are computerized adaptive tests (CATs) available via REDCap, a secure internet application (HealthMeasures, 2021b). Given these QOL measures are CATs, participants were administered different questions and/or a different number of questions (NINDS, 2015). Use of CATs were selected due to their precision (NINDS, 2015).

The Cognitive Function QOL item bank includes 28 questions while the Positive Affect and Well-Being QOL item bank includes 23 questions (NINDS, 2015). Item responses utilize a five-point Likert scale (NINDS, 2015). Despite large question banks, typically less than 5 questions are administered when utilizing CATs (NINDS, 2015). Neuro-QOL measures are estimated to take one minute to complete (HealthMeasures, 2021a). Scoring is completed automatically when using REDCap (HealthMeasures, 2021b). Each QOL measures yield one total score, a T-score (Theta metric), representing QOL in the specific domain assessed. T-scores

and standard errors are provided. According to the NINDS manual, the “score will be produced on the same common (Theta) metric which has been converted to a T-distribution based on the United States general population” (p. 11). Of note, the Cognitive Function QOL item bank includes measures of general concerns and executive function which are then calibrated into one score (NINDS, 2015). According to the NINDS manual, “T-score distributions rescale raw scores into standardized scores with a mean of 50 and a standard deviation (SD) of 10. Thus, a person who has a T-score of 60 is one SD above the average of the referenced [general] populations” (p. 13), therefore, “high scores indicated better (desirable) self-reported health” based on the participants’ subjective report (NINDS, 2015, p. 14).

Procedures

The investigator reviewed inclusion criteria prior to scheduling the participant to complete procedures via remote administration. When scheduling participants, the investigator collected the participant’s email and explained that they would receive a Zoom invite the day before the study and a reminder email the day of the study. Participants were advised to access the link in either email via Zoom to connect with the investigator at the designated day and time. Participants were also informed that they would receive links to a consent form and intake form from via email which they may choose to complete prior to meeting at the scheduled time. These links were generated from REDCap. A copy of the consent form was also sent to the participant as an email attachment. If they chose not to complete these tasks, the consent form was reviewed and intake form was completed with the investigator at the beginning of the procedures. The investigator provided their contact information, including a phone number and email, and advised the participant to contact the investigator with any questions or technical challenges encountered when trying to connect via Zoom.

A protocol script was used to ensure fidelity in protocol administration. All procedures were administered remotely by the same examiner via Zoom, a virtual meeting system (UNCG, 2020). Once connected via Zoom, if the intake form was not completed prior to meeting, the investigator shared their screen and reviewed the consent form. If the participant had previously completed the intake form and read the consent form, the investigator did not review the consent form again. However, consent was always obtained prior to administration of procedures. Participants completed study tasks in the following order: participant intake form, ImPACT, LOFT, QOL measure: Positive Affect and Well-Being, and QOL measure: Cognitive Function. The order of administration remained the same between participants.

While the participant and investigator remained connected via Zoom throughout all procedures, direct administration of tasks either occurred via REDCap (participant intake form, both QOL measures, and the LOFT) or ImPACT Applications Inc. Of note, REDCap is “a secure web application for building and managing online surveys and databases” (REDCap, nd). When administering instruments via REDCap, the participant was sent a link to access the measure via the Zoom chat box. For administration of the ImPACT, a link was sent from ImPACT Applications Inc. to the participant’s email. Again, all tasks were completed while the participant and investigator were connected via Zoom.

The investigator provided guided instructions throughout procedures. The participant was prompted to screen share, allowing the investigator to observe both the participant via Zoom and their screen. During administration of the ImPACT, participants were instructed to skip questions irrelevant to the present study, such as questions regarding concussion history. Participants were also be instructed to skip questions deemed redundant based on study procedures, such as questions regarding self-reported symptoms.

Analysis

Analyses were completed using multiple linear regressions and Pearson's correlations via SPSSv28. The main outcome variables included the following: ImPACT Two-Factor Memory and Speed Composites, the LOFT raw score, and outcome scores from each QOL measure. In total, four multiple linear regressions were run. One multiple linear regression was used to determine the effect of the ImPACT Memory Composite and the LOFT score on QOL in the emotional domain. A second multiple linear regression was used to determine the effect of the ImPACT Speed Composite and the LOFT score on QOL in the emotional domain. A third multiple linear regression was used to determine the effect of the ImPACT Memory Composite and the LOFT score on QOL in the cognitive domain. A fourth multiple linear regression was used to determine the effect of the ImPACT Speed Composite and the LOFT raw score on QOL in the cognitive domain. In addition to the Multiple Linear Regressions, Pearson's correlations were used to determine the relationship between each QOL measure (from the emotional domain and cognitive domain) and each ImPACT Two-Factor Composite score (Memory Composite and Speed Composite). Pearson's correlations were also used to determine the relationship between each QOL measure and the LOFT raw score. In addition, a Pearson's correlation was used to determine the relationship between each ImPACT Two-Factor Composite score (Memory Composite and Speed Composite) and the LOFT raw score. Lastly, Pearson's correlation was used to determine the relationship between length of time since COVID-19 diagnosis and QOL. Length of time since COVID-19 diagnosis was defined as the number of days since receiving a positive COVID-19 diagnosis from a healthcare provider to the date of ImPACT testing. An online calculator (<https://www.timeanddate.com/date/durationresult.html?m1=01&d1=01&y1=2020&m2=01&d2>

=01&y2=2022) was used to calculate the number days between COVID-19 diagnosis and ImPACT testing.

Prior to conducting analyses, data were checked to ensure all assumptions were met. The Speed Composite scores had three outliers. Despite violation of assumptions due to outliers, results are reported both with and without outliers due to the small sample size, as these outliers may represent true variation in performance. Despite effort to include all data, due to a suspected technical error, one participant's ImPACT Speed Composite was excluded from all analyses. While this data point was an outlier, it was excluded from both analyses (i.e., with outliers and without outliers) due to a suspected technical error. Therefore, when results are reported with Speed Composite outliers, only two of the three outliers are included in the analyses ($n = 22$). Analyses were calculated using pairwise deletion in effort to preserve as much data as possible given the small sample size.

CHAPTER IV: RESULTS

QOL and Cognition

QOL: Emotional Domain

A Pearson correlation was used to determine the relationship between QOL in the emotional domain and the ImPACT Two Factor Composite scores: Memory and Speed. QOL in the emotional domain has a small positive association with the ImPACT Memory Composite ($r(21) = .223; p = .305$). When conducting analyses using Speed Composite outliers, QOL in the emotional domain has a medium positive association with the ImPACT Speed Composite ($r(20) = .470; p = .027$). Results were statistically significant when including outliers. However, when outliers were removed from the ImPACT Speed Composite scores, there was no relationship with QOL in the emotional domain ($r(18) = .072; p = .763$).

QOL: Cognitive Domain

A Pearson correlation was used to determine the relationship between QOL in the cognitive domain and the ImPACT Two Factor Composite scores: Memory and Speed. QOL in the cognition domain has a medium positive association with the ImPACT Memory Composite ($r(21) = .388; p = .067$). When conducting analyses using Speed Composite outliers, QOL in the cognitive domain has a medium positive association with the ImPACT Speed Composite ($r(20) = .484; p = .022$). Results were statistically significant when including outliers. When outliers were removed from the ImPACT Speed Composite scores, QOL in the cognitive domain has a small positive association with the ImPACT Speed Composite ($r(18) = .207; p = .381$). However, this relationship did not reach statistical significance.

QOL and Premorbid Verbal IQ

QOL: Emotional Domain

A Pearson correlation was used to determine the relationship between QOL in the emotional domain and premorbid Verbal IQ. QOL in the emotional domain has a no relationship with premorbid Verbal IQ ($r(21) = -.005; p = .982$).

QOL: Cognitive Domain

A Pearson correlation was used to determine the relationship between QOL in the cognitive domain and premorbid Verbal IQ. QOL in the cognitive domain has a small positive association with premorbid Verbal IQ ($r(21) = .204; p = .351$).

Cognitive Performance and Premorbid Verbal IQ

A Pearson correlation was used to determine the relationship between premorbid Verbal IQ and the ImPACT Two Factor Composite Scores: Memory and Speed. Premorbid Verbal IQ has a small positive association with the ImPACT Memory Composite ($r(21) = .211; p = .335$). When conducting analyses using Speed Composite outliers, premorbid Verbal IQ has no relationship with the ImPACT Speed Composite ($r(20) = .026; p = .91$). Similarly, when outliers were removed, premorbid Verbal IQ also had no association with the ImPACT Speed Composite ($r(18) = .056; p = .814$).

QOL and Length of Time Since COVID-19 Diagnosis

QOL: Emotional Domain

A Pearson correlation was used to determine the relationship between QOL in the emotional domain and length of time since COVID-19 diagnosis. QOL in the emotional domain has a small negative association with days since COVID-19 diagnosis ($r(21) = -.251; p = .249$). This relationship did not reach significance.

QOL: Cognitive Domain

A Pearson correlation was used to determine the relationship between QOL in the cognitive domain and length of time since COVID-19 diagnosis. QOL in the cognitive domain has no relationship with days since COVID-19 diagnosis ($r(21) = -.028; p = .901$). Refer to Table 3 for a summary of Pearson’s correlations statistical results and Table 4 for interpretation of Pearson’s correlations.

Table 3. Pearson’s Correlation Statistical Results

Outcome Variables	QOL: Cognitive Domain		QOL: Emotional Domain		LOFT	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
ImPACT: Memory Composite	.388	.067	.223	.305	.211	.335
Impact: Speed Composite without 3 outliers (n=20)	.207	.381	.072	.763	.056	.814
ImPACT: Speed Composite with 2 outliers included (n=22)	.484	.022	.470	.027	.026	.910
LOFT	.204	.351	-.005	.982		
Length of time since COVID-19 diagnosis	-.028	.901	-.251	.249		

Note. *r* = Pearson’s correlation coefficient; *p* = p-value

Table 4. Pearson’s Correlation Interpretation of Results

Outcome Variables	QOL: Cognitive Domain	QOL: Emotional Domain	LOFT
ImPACT: Memory Composite	Medium positive correlation	Small positive correlation	Small positive correlation
Impact: Speed Composite without 3 outliers (n=20)	Small positive correlation	No correlation	No correlation
ImPACT: Speed Composite with 2 outliers included (n=22)	Medium positive correlation	Medium positive correlation	No correlation
LOFT	Small positive correlation	No correlation	
Length of time since COVID-19 diagnosis	No correlation	Small negative correlation	

The Effect of Cognitive Performance and Premorbid Verbal IQ on QOL

QOL: Emotional Domain

A multiple linear regression was used to determine if the ImPACT Speed Composite and premorbid Verbal IQ scores predict QOL in the emotional domain. When conducting analyses using Speed Composite scores outliers, 13.9% of the variance of QOL in the emotional domain can be explained by the ImPACT Speed Composite and LOFT scores. This regression model did not significantly predict QOL in the emotional domain ($F(2, 19) = 2.699, p = .093, \text{adjusted } R^2 = .139$). For each one unit (Z-score) increase in the ImPACT Speed score there is an increase of 2.62 in the QOL score T-score, while each one unit increase in LOFT raw scores result in a decrease of .046 in the QOL score T-score. However, individually, the ImPACT Speed Composite ($t = 2.323, p = .031$) was a significant predictor of QOL in the emotional domain in the present model, while the LOFT score ($t = -.084, p = .934$) was not a significant predictor of QOL in the emotional domain.

When outliers were removed from the ImPACT Speed scores, the regression model did not significantly predict QOL in the emotional domain ($F(2, 17) = .045, p = .956, \text{adjusted } R^2 = -.112$). Each one unit (Z-score) increase in the ImPACT Speed score results in an increase of .781 in the QOL T-score, while each one unit increase in the LOFT raw scores result in a decrease of .024 in the QOL T-score. Neither the ImPACT Speed Composite ($t = .299, p = .768$) nor the LOFT scores ($t = -.037, p = .971$) were significant predictors of QOL in the emotional domain.

In addition, a multiple linear regression was used to determine if the ImPACT Memory Composite and premorbid Verbal IQ scores predict QOL in the emotional domain. This regression model did not significantly predict QOL in the emotional domain ($F(2, 20) = .557, p = .582, \text{adjusted } R^2 = -.042$). Each one unit (Z-score) increase in the ImPACT Memory Score results in an increase of 1.682 in the QOL T-score, while each one unit increase in the LOFT raw scores results in a decrease of .146 in the QOL T-score. As individual predictors in the present model, neither the ImPACT Memory Composite ($t = 1.055, p = .304$) nor LOFT scores ($t = -.245, p = .809$) were significant predictors of QOL in the emotional domain.

QOL: Cognitive Domain

A multiple linear regression was used to determine if the ImPACT Speed composite and premorbid Verbal IQ scores predict QOL in the cognitive domain. When conducting analyses using Speed Composite outliers, 19.4% of the variance of QOL in the cognitive domain can be explained by the ImPACT Speed Composite and LOFT scores. This regression model significantly predicted QOL in the cognitive domain ($F(2, 19) = 3.53, p = .05, \text{adjusted } R^2 = .194$). Each one unit (Z-score) increase in the ImPACT Speed score results in an increase of 3.643 in the QOL T-score, while each one unit increase in the LOFT raw scores results in an increase of .702 in the QOL T-score. However, as individual predictors contributing to the

present model, only the ImPACT Speed Composite score ($t = 2.445, p = .024$) was a significant predictor of QOL in the cognitive domain while LOFT score ($t = .977, p = .341$) was not a significant predictor.

When the outliers were removed from the ImPACT Speed scores, the regression model did not significantly predict of QOL in the cognitive domain ($F(2, 17) = .738, p = .493, \text{adjusted } R^2 = -.028$). Each one unit (Z-score) increase in the ImPACT Speed score results in an increase of 2.886 in the QOL T-score, while each one unit increase in the LOFT raw scores results in an increase of .707 in the QOL T-score. In addition, neither the ImPACT Speed Composite ($t = .843, p = .411$) nor the LOFT scores ($t = .827, p = .42$) were significant predictors of QOL in the cognitive domain.

A multiple linear regression was used to determine if the ImPACT Memory Composite and premorbid Verbal IQ scores predict QOL in the cognitive domain. Based on this model, 8.3% of the variance of QOL in the cognitive domain can be explained by the ImPACT Memory Composite and LOFT. This regression model did not significantly predict QOL in the cognitive domain ($F(2, 20) = 1.99, p = .163, \text{adjusted } R^2 = .083$). Each one unit (Z-score) increase in the ImPACT Memory score results in an increase of 3.528 in the QOL T-score, while each one unit increase in the LOFT raw scores results in an increase of .468 in the QOL T-score. As individual predictors, neither the ImPACT Memory Composite ($t = 1.728, p = .099$) nor LOFT scores ($t = .611, p = .548$) were significant predictors of QOL in the cognitive domain. Refer to table 5 for a summary of multiple linear regression results.

Table 5. Multiple Linear Regression Results

Predictor Variables	QOL: Cognitive Domain		QOL: Emotional Domain	
	<i>p</i>	adjusted R ²	<i>p</i>	adjusted R ²
1. ImPACT: Speed Composite with 2 outliers included (n=22) 2. Premorbid verbal IQ	.05	.194	.093	.139
1. ImPACT: Speed Composite without 3 outliers (n=20) 2. Premorbid verbal IQ	.493	-.028	.956	-.112
1. ImPACT: Memory Composite 2. LOFT	.163	.083	.582	-.042

Note. *p*= p-value

CHAPTER V: DISCUSSION

The present study aimed to determine the relationship between a number of factors including cognitive performance and QOL, premorbid Verbal IQ and QOL, cognitive performance and premorbid Verbal IQ, and length of time since COVID-19 diagnosis and QOL. In addition, this study aimed to determine if cognitive performance and premorbid Verbal IQ predict QOL in either the cognitive or emotional domains in a group of non-hospitalized individuals at least 12 weeks post COVID-19 diagnosis.

Regardless of statistical significance, strength of relationships were reported and discussed in effort to understand trends between outcome variables. However, given the small sample size ($n = 23$), results must be interpreted with caution. Overall, the findings provided inconsistent support for a priori hypotheses. While it was hypothesized that there would be a strong positive relationship between cognitive performance and QOL, analyses revealed primarily small-medium positive relationships between cognitive performance and QOL. While there were positive relationships between objective cognitive performance and QOL, none of the correlations were strong. The relationship between memory performance and QOL was stronger with QOL in the cognitive domain, when compared to QOL in the emotional domain. Despite differences in the strength of association, as memory performance increased, QOL increased in both domains. Given the small sample size, analyses were run both with outliers and without outliers. It is critical to highlight the difference in findings between analyses calculated with and without outliers. Without Speed Composite outliers, there was a small positive nonsignificant relationship between the Speed Composite and QOL in the cognitive domain and no relationship between the Speed Composite and QOL in the emotional domain. Therefore, better performance

on Speed Composite tasks was associated with higher QOL in the cognitive domain. However, when including Speed Composite outliers, both relationships strengthened to a medium positive relationship which reached statistical significance. These findings suggest higher Speed Composite scores were associated with better QOL in both domains.

Findings revealed inconsistent support of the remainder of hypotheses as well. In support of the hypothesis, there was a positive relationship between premorbid Verbal IQ and QOL in the cognitive domain. However, in contrast to the hypothesis, there was no relationship between premorbid Verbal IQ and QOL in the emotional domain. In addition, while it was hypothesized there would be a positive relationship between cognitive performance and premorbid Verbal IQ, this hypothesis was confirmed with the Memory composite, however, not with the Speed composite. Therefore, better memory performance was associated with higher premorbid Verbal IQ. Similarly, while it was hypothesized there would be no relationship between time since COVID-19 diagnosis and QOL, this hypothesis was confirmed with the QOL in the cognitive domain, however, not with the QOL in the emotional domain. The small negative relationship between time since COVID-19 diagnosis and QOL in the emotional domain suggests as time since COVID-19 diagnosis increases, QOL in the emotional domain decreases. Lastly, only one hypothesized model significantly predicted QOL: Premorbid Verbal IQ and Speed Composite scores with outliers predicting QOL in the cognitive domain. However, no additional models reached statistical significance, including the model with Speed Composite scores with outliers removed.

Additional Analyses

Subjective Symptoms

Descriptive statistics were used for further analyses of subjective symptoms reported via the intake form. Despite this study being conducted with non-hospitalized individuals, 74% of participants (17/23) endorsed experiencing at least one new or worsening symptom since testing positive for COVID-19. Surprisingly, if a participant endorsed experiencing any new or worsening symptoms since testing positive for COVID-19, they endorsed central nervous system symptoms (74% of participants). Thirty percent of participants (7/23) endorsed experiencing new or worsening peripheral nervous system symptoms and 26% of participants (6/23) endorsed experiencing new or worsening skeletal muscular injury symptoms since testing positive for COVID-19. Seventeen percent of participants (4/23) reported experiencing new or worsening symptoms in all three categories since testing positive for COVID-19.

The symptom manifestation categories included in the present study were broadly based on the neurologic manifestation categories used by Mao et al. (2020), although specific symptoms in each category varied between studies. Mao et al. (2020) conducted a retrospective observational case series using individuals hospitalized with COVID-19 and found neurological manifestations in 36% of participants (CNS manifestations: 25%, PNS manifestations: 9%, and skeletal muscle injury manifestations: 11%). Supporting the current study's findings, Ding et al. (2020) conducted an electronic survey in a longitudinal study with non-hospitalized individuals ($n = 153$) following COVID-19 and found neurological manifestations were reported in 78% of participants. However, statistics varied from the present study regarding reports of CNS symptoms (47%) versus PNS symptoms (69%) (Ding et al., 2020). Similar to Mao et al. (2020), specific symptoms in each category varied from the current study, which may explain the

difference in findings from the present study. For example, Ding et al. (2020) included impairment in taste and smell as PNS manifestations. It should also be noted, only 11% of participants had symptoms lasting more than 8 weeks after symptom onset (Ding et al., 2020). The symptoms endorsed by non-hospitalized individuals following COVID-19 highlight neurological symptoms are not dependent on hospitalization status.

Performance on Study Tasks

On average, non-hospitalized individuals in the chronic phase of disease progression following COVID-19 reported higher levels of positive affect and well-being, or QOL in the emotional domain (average T-score= 54.1; range= 43.5-66.7), when compared to subjective report of cognitive function, or QOL in the cognitive domain (average T-score= 40.86; range= 24.5-57). While the average self-reported QOL measured in the emotional domain was approximately .5 a standard deviation higher than the mean from the US general population, the average self-reported QOL measured in the cognitive domain was approximately 1 standard deviation below the mean from the US general population. There was a large difference in range of scores when comparing QOL outcomes between measures. The variation in QOL outcomes was greater when measured via QOL in the cognitive domain versus QOL in the emotional domain. The range in T-scores yielded from QOL in the emotional domain only ranged from approximately .5 a standard deviation below to 1.5 standard deviations above the US general population mean. In comparison, QOL in the cognitive domain ranged from approximately 2.5 standard deviations below to less than 1 standard deviation above the US general population mean.

On average, non-hospitalized individuals in the chronic phase following COVID-19 scored slightly below the normative sample based on the ImPACT Memory Composite (average

calculated Z-score= -.1; range= -1.56- 1.65). The Memory Composite scores ranged from approximately 1.5 standard deviations below to 1.5 standard deviations above the normative sample mean. Cognitive function varied based on the ImPACT Speed Composite scores calculated with (average calculated Z-score with outliers= -.15; range with outliers= -4.09-1.02) and without outliers (average calculated Z-score without outliers= .124; range without outliers= -1.12-1.02). The average ImPACT Speed Composite was slightly below the normative sample when outliers were included, versus being slightly above the normative sample when outliers were removed. The Speed Composite without outliers ranged from approximately 1 standard deviation below the normative sample mean to 1 standard deviation above the mean. However, with outliers included, the Speed Composite ranged from over 4 deviations below the mean to 1 standard deviation above the mean. While premorbid Verbal IQ scores were not reported in comparison to a normative sample, the average raw LOFT score was 44.5 (range= 39 to 48).

Length of Time Since COVID-19 Diagnosis

If a disease such as COVID-19 impacts quality of life, one would expect changes or fluctuations in quality of life during the acute and subacute phases following disease onset. However, once an individual reaches the chronic phase following disease progression, it is reasonable to expect the impact from disease on QOL stabilizes. One potential explanation for reduced QOL over time could be due to cognitive function. Perhaps one may suspect: if cognition declines with time, functional impairments may lead to reduced QOL over time. Therefore, additional analyses were run to determine the relationship between cognitive function and time since COVID-19 diagnosis. Findings revealed a small positive relationship between days since COVID-19 diagnosis and the Memory Composite ($r = .290, p = .180$), a medium positive relationship between days since COVID-19 diagnosis and Speed Composite scores

including outliers ($r = .414, p = .056$), and a strong positive relationship between days since COVID-19 diagnosis and Speed Composite scores without outliers ($r = .523, p = .018$). While the strength of association varied, all three analyses revealed a positive relationship between days since COVID-19 diagnosis and cognitive function. These findings suggest as time increases during the chronic phase following COVID-19, cognitive function improves. Given the positive relationships between cognitive function and QOL in the cognitive domain paired with the positive relationships between cognitive function and time since COVID-19 diagnosis, one may expect a relationship between time since COVID-19 diagnosis and QOL in the cognitive domain. However, the present study found no relationship between time since COVID-19 diagnosis and QOL in the cognitive domain. Ultimately, the positive relationship between time since COVID-19 diagnosis and cognitive function does not help explain the negative relationship between time since COVID-19 diagnosis and QOL in the emotional domain. Additional research is warranted to better understand the relationship between time since COVID-19 diagnosis and QOL.

Measurement Instruments

The relationship between cognitive performance and QOL varied based on the cognitive area tested (memory versus speed) and QOL domain assessed (cognitive versus emotional). For example, there were stronger relationships between cognitive performance (i.e., Memory Composite and Speed Composite with outliers removed) and QOL in the cognitive domain, versus cognitive performance and QOL in the emotional domain. One potential explanation for the stronger relationships between objective cognitive performance and QOL in the cognitive domain is that this QOL instrument measures perceived cognitive abilities. For example, the Neuro-QoL Cognitive Function domain is defined as “Perceived difficulties in cognitive abilities (e.g., memory, attention, and decision making, or in the application of such abilities to everyday

tasks (e.g., planning, organizing, calculating, remembering and learning)” (NINDS, 2015, p. 6). Given this instrument was based on perceived cognitive abilities, it was surprising that results did not uncover stronger relationships between cognitive performance and QOL in the cognitive domain. However, these findings support previous literature documenting a discrepancy between subjective and objective cognitive function. For example, Almeria et al. (2020) found that performance on cognitive tasks did not differ between individuals who reported cognitive impairment (34% of participants) versus individuals who did not report cognitive impairment following COVID-19. Similarly, Albu et al. (2021) report, “reporting subjective cognitive complains was unrelated to altered cognitive tests” (p. 472).

When comparing the relationship between objective cognitive function and fatigue-based QOL versus cognition-based QOL, Graham et al. (2021) found: “fatigue-based quality of life was more clearly correlated with NIH Toolbox cognitive function” (p. 9). Graham argues that this may suggest reduced insight into QOL in the cognitive domain when compared to fatigue-based QOL. Similarly, in the present study, the lack of strong positive relationship found in the present study may suggest poor insight to cognitive function.

Perhaps another potential reason why there was not a strong relationship between objective cognitive performance and QOL in the cognitive domain is that objective cognitive performance was measured in specific cognitive areas from the ImPACT: memory and speed performance, while the QOL measure item bank included questions on perceived cognitive abilities in a variety of cognitive areas: memory, attention, and executive function. The QOL measure item bank had more questions in which responses would be impacted by memory deficits versus speed deficits. However, the first question always asked about the individual’s reaction time. In comparison, memory questions were often not included. The QOL measure was

a computerized adaptive test and therefore the questions provided varied between participants and the items administered were based on previous responses. Since participants received different questions, the questions asked could have varied in their breadth and depth of tapping into various cognitive areas. Lastly, given the stronger relationship between the Memory Composite and QOL in the cognitive domain, it is possible that memory impairments have a greater impact on functional activities when compared to speed impairments, which in turn may affect insight to deficits and QOL.

The specific emotional health measure used in this study was the domain *Positive Affect and Well-Being*. This domain is defined as “aspects of a person’s life that related to a sense of well-being, life satisfaction or an overall sense of purpose and meaning” (NINDS, 2015, p. 6). The findings of a small positive association between QOL in the emotional domain and the Memory Composite but no relationship between QOL in the emotional domain and Speed Composite scores without outliers may suggest memory performance has a greater impact on QOL in emotional health. Although, when including outliers, the relationship between the Speed Composite and QOL in the emotional domain became stronger than the relationship between QOL in the emotional domain and the Memory Composite.

The variation in findings based on the QOL measures used and cognitive areas assessed highlight the importance of utilizing instruments with optimal sensitivity and specificity to detect the subtle impairments associated with COVID-19. Instruments utilized to assess cognition have varied greatly among the COVID-19 literature and include: Mini-Mental State Examination (Alemanno et al., 2021; Negrini et al., 2020), Montreal Cognitive Assessment (MoCA) (Alemanno et al., 2021; Raman et al., 2021), Continuous Performance Test (Zhou et al., 2020), Digit Span Test (Zhou et al., 2020), Digits Forward and Backward (Almeria et al., 2020), and

Trail Making Test (Almeria et al., 2020; Zhou et al., 2020). Similarly, QOL measures have varied among COVID-19 literature. For example, Poudel et al. (2021) conducted a rapid review of studies looking at the effect of COVID-19 on health-related quality of life (HRQoL) and found “The majority of the studies (n = 10) used generic HRQoL assessment tool (five used SF-36, five EQ-5D-5L), and the rest used a pulmonary disease-specific HRQoL tool, i.e. SGRQ (St George’s Respiratory Questionnaire) tool (2/12), Clinical COPD Questionnaire (CCQ) (1/12), and PROMIS tool (1/12)” (p. 6).

The wide array of instruments used limit comparison of findings across studies. For example, while the medium strength of association between memory and QOL in the cognitive domain appears to support previous literature documenting a significant moderate correlation between working memory assessed via the NIH Toolbox and PROMIS cognition QOL in non-hospitalized COVID-19 long haulers (Graham et al., 2021), the direction of these relationships varied. In contrast to the present findings, Graham et al. (2021) found an inverse relationship between working memory and QOL based on Spearman’s correlation (Graham et al., 2021). Memory was the only cognitive area significantly correlated with the PROMIS cognition QOL measure (Graham et al., 2021). No correlation was found between the PROMIS cognition QOL and processing speed measured via the NIH Toolbox. Perhaps the difference in findings between the current study and Graham et al. (2021) are due to the variation in instruments used.

In addition, Graham et al. (2021) found all participants (individuals who tested positive and negative for SARS-CoV-2) scored significantly worse than the normative population for QOL in the domains of cognition and fatigue (Graham et al., 2021). QOL scores pertaining to fatigue were moderately related to the following: processing speed, executive function, and working memory (Graham et al., 2021). Similarly, Bungenberg et al. (2021) found increased

fatigue was related to reduced psychomotor speed and attention, and fatigue severity was significantly related to lower QOL as measured via the EQ5D. Lower performance on measures of psychomotor speed and attention were also related to lower scores on the EQSD (a health status measure for quality of life) (Bungenberg et al., 2021). These findings highlight the need for additional research to determine which measures of cognition and QOL are optimal to use following COVID-19.

Cognitive Reserve

As previously discussed, premorbid IQ has been used as a proxy for cognitive reserve (Steward et al., 2018). Therefore, the small positive relationship between memory performance and premorbid Verbal IQ may suggest cognitive reserve is associated with memory performance. If so, premorbid Verbal IQ may serve as a protective factor against memory impairment as higher premorbid Verbal IQ appears associated with better memory function following COVID-19.

Consistent with our findings, Steward et al. (2018) found higher premorbid IQ, or greater cognitive reserve, was related to better memory function in individuals with traumatic brain injury and healthy controls. In addition, cognitive reserve and verbal memory were found to have a large significant relationship in individuals with MS (Sumowski et al., 2009). However, contrasting our findings, higher premorbid IQ, or cognitive reserve, was also related to better processing speed/executive functioning (Steward et al., 2018). Findings from the present study revealed no relationship between premorbid Verbal IQ and current Speed Composite with or without outliers.

Gu & Xu (2022) conducted a meta-analysis on cognitive reserve and found, “higher education levels were related to better general cognitive function, executive function, memory,

and information processing speed in PD patients” (p. 3). Similar to previous studies discussed, this literature supports the positive relationship between premorbid Verbal IQ, or cognitive reserve, and memory function. However, Gu & Xu’s (2022) findings contrast the present study findings of no relationship between premorbid Verbal IQ, or cognitive reserve, and speed function.

The relationship between premorbid Verbal IQ and cognitive function varied based on the specific cognitive area assessed (i.e., memory versus speed). Given the inconsistent relationships, it is possible premorbid Verbal IQ, or cognitive reserve, provides a different level of protection against cognitive decline in certain cognitive areas.

Similarly, the relationship between premorbid Verbal IQ and each QOL measure varied. Findings revealed a small positive relationship between premorbid Verbal IQ scores and QOL in the cognitive domain, suggesting an increase in premorbid Verbal IQ is associated with an increase in QOL in the cognitive domain. While correlations do not imply causation, discussion of individual dichotomous relationships may provide a larger context to the understand the intertwined nature of multiple variables. For example, it is possible the small positive relationship between premorbid Verbal IQ and memory performance is driven by the protective factor of cognitive reserve. Subsequently, there was also a small positive relationship between memory and QOL in the cognitive domain. Therefore, these findings may suggest higher cognitive reserve is serving as a protective factor against memory decline, and therefore related to increased QOL in the cognitive domain.

If premorbid Verbal IQ is viewed as a proxy for cognitive reserve, there appears to be no relationship between cognitive reserve and QOL in the emotional domain. These findings suggest there is no relationship between premorbid Verbal IQ and QOL pertaining to one’s

perceived well-being, satisfaction of life, or perceived purpose. The lack of relationship is surprising given the relationship between premorbid Verbal IQ and QOL in the cognitive domain.

Cognition: Speed

Only one regression model reached statistical significance to predict QOL. When conducting analyses with outliers included, Speed Composite and premorbid Verbal IQ were found to predict QOL in the cognitive domain. When controlling for premorbid Verbal IQ, the Speed Composite contributed significantly to the model. Findings from previous literature documenting cognitive reserve moderating information processing efficiency outcomes in individuals with MS may help explain this model (Benedict et al., 2010). Benedict et al. (2010) explains, “Patients with low reserve were likely to show decline over time, especially on the [Symbol Digit Modalities Test- a measure of processing speed,], whereas those with high [cognitive reserve] did not.” (p. 832). The current study findings may also be explained by the relationships found between each independent variable and QOL in the cognitive domain. For example, there was a medium significant positive relationship between the Speed Composite scores computed with the outliers and QOL in the cognitive domain, and a small positive relationship between premorbid Verbal IQ and QOL in the cognitive domain. However, there was no relationship between the Speed scores (with outliers) and premorbid Verbal IQ.

The relationship between the Speed Composite scores with outliers included and QOL in the emotional domain revealed a medium positive relationship which reached statistical significance. However, the relationship between premorbid Verbal IQ and QOL in the emotional domain had no relationship, which may explain why this regression model did not reach statistical significance.

Although it is expected that findings from analyses calculated with Speed scores with outliers versus without outliers would vary, it was surprising that analyses calculated with Speed outliers often resulted in statistically significant findings. Literature on speed in various populations has yielded interesting findings. For example, McMillan et al. (2021) found “Slowing of cognitive and psychomotor processing speed, a long recognized cognitive complication of the epilepsies, exhibits an impressive mediational role across several critical domains of higher cognitive function including immediate memory, delayed memory, executive function, and working memory.” (p. 8). McMillan et al. (2021) proceed by explaining the mediational role was not found in controls. Ferrucci et al. (2021) assessed cognition in hospitalized COVID-19 patients on average 4.4 months post discharge. Findings revealed impairments in processing speed in 42% of participants (Ferrucci et al., 2021). Additional research is warranted using speed tasks in individuals with COVID-19.

To better understand underlying factors which may account for the significant regression model, additional analyses were completed on the components which comprise the Speed Composite from the ImPACT. A discussion of the Speed Composite from the ImPACT, as well as an in-depth discussion of the Speed Composite outliers are included below.

ImPACT: Speed Composite

As previously discussed, the Speed Composite is calculated based on computed Z-scores from the Visual Motor Speed and Reaction Time Core Composite scores. According to the ImPACT Applications, Inc. manual (2021a), the Visual Motor Speed Composite “Evaluates visual processing, learning and memory, and visual-motor response speed” (p. 15), while the Reaction Time Composite “Evaluates average response speed” (p. 16). The equation used to determine the Visual Motor Speed Composite is calculated based on the number of correct

responses from “a choice reaction time test” (ImPACT Applications, Inc., 2021a, p. 10) and the mean number of correct responses (i.e., selected numbers) on a speed task (ImPACT Applications, Inc., 2021a). The equation used to determine the Reaction Time Composite is calculated based on the mean reaction time on specific components from three subtests included in the ImPACT (ImPACT Applications, Inc., 2021a, p. 13). Since the Speed Composite (with outliers included) was found to be a significant predictor of QOL in the cognitive domain when controlling for premorbid Verbal IQ, additional analyses are warranted to better understand how the Core Composites that comprise the Two-Factor Speed Composite relate to QOL.

A Pearson’s correlation was calculated between each of the Core Composite scores that contribute to the Speed Composite, and each measure of QOL. Reaction Time Composite scores have a medium negative relationship with QOL in the cognitive domain (Pearson correlation= -.495; $p = .019$) and strong negative relationship with QOL in the emotional domain (Pearson correlation= -.519; $p = .013$). Higher Reaction Time composite scores indicate worse performance. Therefore, as reaction time increases, or gets worse, QOL decreases. Visual Motor Speed Composite scores have a medium positive relationship with QOL in the cognitive domain (Pearson correlation= .355; $p = .097$) and a small positive relationship with QOL in the emotional domain (Pearson correlation= .216; $p = .322$). Higher Visual Motor Speed Composite scores indicate better performance. Therefore, these findings suggest as visual motor speed increases, QOL increases.

When comparing the relationships between each of these core composite areas and QOL, stronger relationships were found between Reaction Time and each QOL measure. In addition, the correlations between Reaction Time and each QOL measure reached statistical significance, while the correlations between Visual Motor Speed and each QOL measure did not. Given these

findings, it appears Reaction Time may have been an underlying factor contributing to the Speed Composite being a significant predictor of QOL.

It is important to note that the core composite analyses were calculated with all data from the Visual Motor Speed Composite scores ($n = 23$). However, one participant's Reaction Time Composite score was removed prior to analyses ($n = 22$) due to a suspected technical error. Despite three outliers found in the Reaction Time Composite scores and one outlier found in the Visual Motor Speed Composite scores; these outliers were included in analyses since the significant regression model was yielded from analyses calculated with the Speed Composite outliers included.

Additional analyses using descriptive statistics were used to better understand objective speed performance versus self-reported speed function. Despite the Neuro-QOL Cognitive Function measure being a computerized adaptive test, the first question always asked participants about self-reported speed function. The first item read: "In the past 7 days I reacted slowly to things that were said or done". Responses ranged on a 5-point scale from *Never* to *Very Often (several times a day)*. Inconsistencies were found when comparing perceived reaction time from the QOL measure to the ImPACT Speed Two-Factor score. For example, six individuals either responded *Often (once a day)* or *Very Often (several times a day)* when asked if they reacted slowly to things within the past week. However, of these six individuals, based on ImPACT Speed Two-Factor scores only two scored below the normative sample mean. Four individuals who endorsed reacting slowly to things either once a day or several times a day scored above the normative sample mean based on the ImPACT Speed Two-Factor score (range of ImPACT Speed Two-Factor scores for these four participants self-reporting reacting slowly to things at least once a day = .06-.59). Surprisingly, the participant with the lowest ImPACT Speed Two-

Factor score (-4.09) only endorsed perceived slow reaction times *sometimes* (two to three times within the past week). Refer to table 6 for a comparison of objective versus subjective reports of cognitive speed.

Table 6. Cognitive Speed: Objective Performance versus Subjective Report

Objective Performance ImPACT Speed Two-Factor Score	Subjective report: <i>In the past 7 days I reacted slowly to things that were said or done</i>				
	Never	Rarely (Once)	Sometimes (2-3 times)	Often (Once a day)	Very Often (Several times a day)
-4.09			x		
-1.72					x
-1.12				x	
-0.98			x		
-0.52	x				
-0.3			x		
-0.23			x		
-0.19		x			
0.01		x			
0.06					x
0.1				x	
0.13					x
0.14	x				
0.27			x		
0.27			x		
0.44		x			
0.47			x		
0.56	x				
0.59				x	
0.84		x			
0.92		x			
1.02			x		

Note. According to the ImPACT Applications, Inc. manual (2021a), “The Two-Factor Scores are calculated as Z-scores (subtracting the user’s score from the group mean and dividing by the standard deviation: $(X - \text{Mean}) / \text{SD}$) and are presented as percentile ranks. ... the Speed Composite is calculated by subtracting the Motor Speed and Reaction Time Z-scores and dividing by 2...”

(p. 17). Given the Two-Factor Scores are calculated as Z-scores, higher scores indicate better performance.

ImPACT: Speed Composite Outliers

Although it is expected that findings yielded from analyses calculated with Speed Composite scores with outliers versus without outliers would vary, it was surprising that analysis calculated with Speed Composite outliers often yielded statistically significant findings. For example, when Speed Composite outliers were included in analyses, there was a statistically significant relationship between Speed Composite scores and QOL in both domains. These were the only Pearson's correlations to reach statistical significance. In addition, the overall regression model using Speed Composite scores with outliers included significantly predicted QOL in the cognitive domain. Therefore, a discussion is warranted to better understand the Speed Composite outlier performance and how these data points may have influenced findings.

Throughout this study, analyses calculated with Speed Composite outliers included data from 22 of the 23 participants. As previously explained, one participant's Speed Composite score was removed prior to analyses due to a suspected technical error. While this participant's Speed Composite score was technically an outlier, this data point was not included in any analyses reported. Therefore, the following will only include a discussion of the outliers whose data were included in the Speed Composite data with outliers included.

The Speed Composite had two outliers whose performance warrant further discussion. Both outliers reported poor levels of QOL. For example, these participants tied for having the lowest scores for QOL in the emotional domain, with scores falling approximately one standard deviation below the US general population mean (T-scores= 43.5). In addition, these participants had the second (T-score= 27.7) and third (T-score=28.5) lowest scores for QOL in the cognitive

domain. Both outliers scored more than two standard deviations below the mean cognitive domain QOL scores from the US general population.

With regard to ImPACT Core Composite scores, one outlier had the lowest percentile rating for the ImPACT Memory Composite Visual score (<1%) and the lowest percentile rating for the ImPACT Visual Motor Speed Composite score (2%). The outliers had the two lowest percentile ratings for the Reaction Time Composite (1% and <1%). Surprisingly, premorbid Verbal IQ levels varied between participants. One outlier had the lowest raw score for the LOFT (39/50) while the other did well on the LOFT (47/50).

One outlier reported being color blind on the ImPACT, however, this was not suspected to have affected performance on the ImPACT. This participant scored in the first percentile for the reaction time composite, which considers the reaction time from a color match task in which the respondents click if the color of the word matches the written word (ex. “Red” is written in red text). The participant did not have any commissions on this task, and therefore it was not suspected that color vision impacted results. In addition, the reaction time composite is comprised of two additional scores, and color vision is not suspected to have influenced performance on these tasks. However, it is possible that color vision may have influenced these outcomes from the ImPACT. It is critical to note that the participant subjectively endorsed experiencing slow reaction times. For example, when the QOL measure prompted, “In the past 7 days I reacted slowly to things that were said or done”, the participant responded, “Very Often (several times a day)”. Refer to table 7 for this participant’s scores on the ImPACT core composite areas.

Table 7. Participant Performance: Outlier 1 Speed Composite

Composite Areas	Composite Score	Percentile
Memory composite (verbal)	77	18%
Memory composite (visual)	63	23%
Visual motor speed composite	30.38	22%
Reaction time composite	.96	1%

The second outlier reported being prescribed ADHD medication to treat brain fog secondary to COVID-19. However, this participant denied history of ADHD. Interestingly, when the QOL measure prompted, “In the past 7 days I reacted slowly to things that were said or done”, the participant responded, “Sometimes (2-3 times)”. Refer to table 8 for this participant’s scores on the ImPACT core composite areas.

Table 8. Participant Performance: Outlier 2 Speed Composite

Composite Areas	Composite Score	Percentile
Memory composite (verbal)	87	32%
Memory composite (visual)	27	<1%
Visual motor speed composite	19.05	2%
Reaction time composite	1.28	<1%

The participant intake form included three questions inquiring about subjective reports of new or worsening symptoms since testing positive for COVID-19. These three questions inquired about symptoms groups into central nervous system, peripheral nervous system, and skeletal muscular injury manifestations. Both Speed Composite outliers endorsed new or worsening symptoms in all three of these areas since testing positive for COVID-19. Further analyses of participant responses regarding subjective symptoms are included below.

Based on overall performance across tasks, it is suspected that these Speed Composite outliers reflect true variation in performance on Speed tasks due to cognitive deficits secondary

to COVID-19. However, additional research is warranted to validate present study findings and better understand impact of COVID-19 on cognitive function.

Limitations

The largest limitation of this study was the small sample size ($n = 23$) which impacted interpretation of findings. Recruitment of participants was particularly challenging. While effort was made to recruit from the general public, many participants were recruited from Facebook groups for individuals with COVID-19. Therefore, it is questioned if the sample is truly representative of the general public as these individuals may be more likely to have experienced persistent symptoms and reduced QOL following COVID-19.

Remote administration of tasks provides many benefits, one being the ability to expand recruitment efforts beyond one geographic location. However, there were also limitations associated with remote administration of procedures. For example, the investigator was unable to control the environment (i.e. testing location/environment, questionable focus given to instructions, one participant requiring prompting to refrain from using an external memory aid during a task), control for environmental distractors (i.e. disruptions from other people, eating or drinking during study, notifications on computers, computer settings/tabs opened etc.), general technology challenges (i.e. inability to screen share, screen freezing/glitching impacting ability to see participant during tasks, inability for participant's video or audio to connect via the computer resulting in connection of Zoom video via cell phone while screen sharing occurred via the computer), and electronic testing challenges (i.e. computer appearing to freeze during a timed task, pop up during a timed task, a clicked response not appearing to register initially during a speed task). Technology challenges even resulted in participants having to meet with the

investigator a second time for completion of study tasks on occasion. In addition, at times it was questioned if participants were taking the time to read the instructions thoroughly.

It should be noted that three participant's ImPACT clinical reports were flagged for potential invalid testing. However, this was disregarded for purposes of the present study. The baseline test is typically given prior to concussion as a baseline measure of cognitive performance. Therefore, it is plausible that participants performance was flagged due to true impairment secondary to COVID-19 demonstrated on the baseline test. Interestingly, one participant responded "yes" to all delayed design memory questions, yet this individual's performance was not flagged as invalid.

An additional limitation is that this study relied on the participant self-reporting their date of positive COVID-19 diagnosis from a healthcare provider. Four unique situations arose requiring best judgement to estimate days since positive COVID-19 diagnosis. For example, one participant appeared to provide the wrong year (i.e., reported a date in the future), one participant provided multiple dates of positive COVID-19 diagnoses, and two participants did not include the full date of positive COVID-19 diagnosis (i.e., month/day/year). Requiring healthcare documentation of a positive COVID-19 diagnosis would eliminate self-reporting errors. However, this solution also comes with limitations as it would place a greater burden on participants volunteering for this study to retrieve a copy of their COVID-19 documentation.

Limitations related to the collection of subjective symptoms from the intake form warrant discussion as well. Symptom questions asked, "Are you experiencing any of the following new or worsening symptoms since testing positive for COVID-19?" It is possible that someone responded *yes*, however, the symptom experienced was not directly caused by COVID-19. In addition, the intention of the question was to obtain subjective symptoms currently experienced

by the individuals to determine symptoms experienced in the chronic phase of COVID-19. However, one participant inquired if these questions are asking about current symptoms or symptoms experienced following COVID-19 that have since resolved. In this specific circumstance, the individual was prompted to respond however they interpret the question, and the provided responses were used for analysis since it is possible other participants interpreted the question the same way. However, the participant responded “yes” to a question but said that the symptom was an acute symptom that resolved, and they are no longer experiencing the symptom.

Despite effort to control for comorbidities through extensive inclusion criteria, limitations persisted. The present study did not control for medications and, therefore, one potential limitation is the possibility that a medication impacts cognitive performance. For example, one participant reported being prescribed ADHD medication to treat brain fog secondary to COVID-19.

A couple of participants reported other potential variables outside of COVID-19 that could be impacting their QOL. One limitation is that even though this study assessed the relationship between cognition and QOL, QOL may be affected by a multitude of variables outside of COVID-19. However, this study never sought to make statements regarding causation, only correlations. Regardless, it is important to highlight that the QOL measures did not assess QOL specifically due to COVID-19.

Other limitations persist given the rapid development of COVID-19. For example, since the start of this study, additional variants of COVID-19 have been identified. It is possible that certain variants of COVID-19 directly affect symptoms and long-term effects following disease progression. COVID-19 vaccinations have also become more prevalent since the start of this

study. It is possible that vaccination status may influence long-term symptoms experienced following COVID-19. In addition, future studies should inquire about the number of times individuals tested positive for COVID-19 as re-occurrence of infection has become more prevalent over time.

Clinical Implications

While the small sample size limits interpretation of findings, clinicians are encouraged to assess cognitive function and include an objective and/or subjective measure of speed performance (i.e., reaction time) when assessing individuals following COVID-19. Clinicians are also encouraged to provide QOL measures to patients presenting with cognitive deficits secondary to COVID-19. Providing a measure such as the Neuro-QOL Item Bank v2.0 - Cognitive Function has the potential to reveal functional impairments that are challenging to assess via traditional cognitive measures. In addition, findings from QOL measures may provide clinicians with information regarding the patient's insight to cognitive deficits. When QOL measures are provided, clinicians should use findings to inform treatment approaches for maximum functional gains. In summary, clinicians should be mindful that cognitive deficits and reduced QOL may persist in non-hospitalized individuals following COVID-19 and cognitive deficits may impact QOL despite hospitalization status.

Future Directions

Despite literature on the long-term impact of COVID-19 rapidly accumulating, multiple gaps in the literature remain. More specifically, gaps in the literature remain in studies conducted exclusively on non-hospitalized individuals following COVID-19. Given the small sample size limiting interpretation of findings, current study procedures should be replicated using a larger sample recruited from the general public to better understand the relationship between cognition

and QOL. In the future, measures of objective cognitive performance should be expanded (i.e. attention, executive function) to determine their relationship with QOL. In addition, longitudinal studies are necessary to understand the progression of cognition and QOL following COVID-19. Once cognitive and functional consequences of COVID-19 are better understood, research should focus on treatment approaches to best address these cognitive deficits. Additional research is urgently warranted to better understand the relationship between cognition and quality of life in non-hospitalized individuals in the chronic phase following COVID-19 recruited from the general public.

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