Relationships between Domain-specific Cognitive Function, Functional Performance and Life Satisfaction in Persons with Chronic Obstructive Pulmonary Disease (COPD)

By

Julie Ann Slack

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Nursing)
in the University of Michigan
2018

Doctoral Committee:

Professor Janet Larson, Chair
Professor Bruno Giordani
Professor Jacqui Smith
`` Clinical Associate Professor Laura Struble

Julie Ann Slack

jagrider@umich.edu

ORCID iD: 0000-0002-2670-6082©

DEDICATION

"Nothing is Impossible. The word itself says I'm possible"

Audrey Hepburn

This work is dedicated to the many exceptional people that have been my constant pillars of strength and encouragement. To my parents, Robert and Joyce Slack, who have always loved me unconditionally and taught me that I could achieve whatever I set my mind to accomplish. To my children, Sarah and Matthew, who have sacrificed and helped me in countless ways. To my brother Ric, who thought my degree should have been M.D., supported me on my journey and ensured that I had the peace and tranquility of star filled nights in the middle of the Great Lakes to maintain my sanity. And to my dear friend, Geff, who not only encouraged me to return and finish my degree but at a great cost helped me to be the strong person I once was. I am so blessed to have you in my heart and life. And I am forever indebted to every one of you. Meet in me Panama City, Florida in November because I'm Possible.

ACKNOWLEDGMENTS

My thanks and appreciation to my dissertation committee, Dr. Janet L. Larson, Dr. Bruno Giordani, Dr. Jacqui Smith and Dr. Laura Struble. They have generously given their time and expertise to better my work. I thank them for all their contributions.

Special appreciation and thanks to MaryKay Hanby for assistance in the recruitment of subjects for my pilot study.

PREFACE

The dissertation "The Relationships between Domain-Specific Cognitive Function, Functional Performance and Life Satisfaction in Persons with Chronic Obstructive Pulmonary Disease (COPD)" is a three-paper dissertation to partially fulfill the graduation requirements of the University of Michigan School of Doctor of Philosophy in Nursing.

The inspiration for the subject came from the man that was my sailing mentor. After smoking two packs of cigarettes daily for the past 62 years, he developed COPD. With the progression of COPD, decisions to call tactics took longer and now so much strength has left his body he can no longer sail. He has become a power boater to continue to enjoy being on the water. I was curious if others with COPD had similar experiences in which there was a change in cognition and the loss of strength that led to lifestyle changes to maintain activities of enjoyment. My research questions were formulated together with my committee chair, Dr. Janet L. Larson.

The research questions were answered through three papers; a systematic review and meta- analysis, a secondary data analysis and a pilot study using the National Institute of Health Cognitive Toolbox and PROMIS® to begin to explain the relationships between domain-specific cognition, functional performance and life satisfaction in persons with COPD.

Julie Slack

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Activities of daily living (ADLs)

Center for Epidemiological Studies-Depression (CES-D)

Chronic Obstructive Airway Disease (COAD)

Chronic Obstructive Pulmonary Disease (COPD)

Computerized Adaptive Testing (CAT)

Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)

Forced Expiratory Volume in one minute (FEV_1)

Global Initiative for Chronic Obstructive Lung Disease (GOLD COPD)

Health and Retirement Study (HRS)

Institute of Social Research (ISR)

Instrumental activities of daily living (IADLs)

Mild cognitive impairment (MCI)

Mini-Mental Status Exam (MMSE)

modified Medical Research Council Dyspnea scale (mMRC)

National Health and Nutrition Examination Survey (NHANES)

National Institute of Health (NIH)

National Institute of Health Toolbox (NIHTB)

National Institute of Health Toolbox Cognitive Battery (NIHTB-CB)

National Institutional of Aging (NIA)

Nocturnal Oxygen Therapy Trial (NOTT)

Patient Reported Outcomes Measurement Information System (PROMIS®)

Selection, Optimization and Compensation (SOC)

Standard Mean Differences SMD)

Trailmaking Test A (TMT-A)

Trailmaking Test B (TMT-B)

United States (U.S.)

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of disability. Not only does COPD cause breathing difficulties, there are extrapulmonary effects including cognition with domain-specific cognition as our primary focus. Evidence suggests that COPD has negative effects on domain-specific cognition which may be related to declines in functional performance and life satisfaction. This three-paper dissertation includes a) a meta-analysis summarizing the effect size of changes in domain-specific cognition, b) a secondary analysis of the HRS data set examining longitudinal changes in domain-specific cognition in persons with and without COPD and c) a pilot study examining feasibility and acceptability computerized adaptive testing CAT) in persons with COPD and describing a preliminary relationship between domain-specific cognition, functional performance and life satisfaction. In the meta-analysis, differences indicated that persons with COPD had poorer performance than persons without COPD. No difference was found between the groups in the domains of executive function measured with verbal fluency animal or language measured with Boston Naming. A small effect size was found in memory and learning measured with Digit Span Forward (-0.298, 95% CI [-0.480 - -0.114], $p < 0.001$) and executive function measured with Digit Span Backward (-0.352, 95% CI [-0.105 – - 2.80], $p < 0.001$). Moderate effect sizes were found in attention measured with Trailmaking Test A (TMT-A) (-0.516, 95% CI [-0.747 – -0.286], $p < 0.001$), in memory and learning measured with Wechsler Memory Scale immediate recall (-0.6, 95% CI [-0.480 – -0.114], $p < 0.001$) and delayed recall (-0.420, 95% CI [-0.610 – - 0.231], $p < 0.001$); in executive function

Measured with Trailmaking Test B (TMT-B) (-0.571, 95% CI [- 0.769 - - 0.374], $p < 0.001$) and large effect sizes were found in executive function measured with verbal letter fluency (-0.746, 95% CI [- 0.961 - - 0.530], $p < 0.001$) and processing speed measured with digit symbol (-0.923, 95% CI [-0.769 - -0.374], $p < 0.001$). In the secondary data analysis, persons with COPD had significantly poorer performance in executive function and memory and learning. Both groups had significant declines over time, with a steeper decline immediate recall in the non-COPD group. In cross-sectional analysis, persons with COPD, no significant relationships between the cognitive domains and life satisfaction to mediate. In the non-COPD group, there was a relationship between delayed recall and life satisfaction that was fully mediated by activities of functional performance. Hopelessness explained a significant portion of the variance in cognition in both groups. Semipartial in the COPD group, hopelessness uniquely contributed to immediate recall (7%) and delayed recall (9%) and explained very little in the non-COPD group (<1%). Finally, a pilot study examined feasibility and acceptability of computer adaptive testing (CAT) in COPD. On a scale of 0 - 5, the CAT had a 4.3 overall impression indicating acceptability. Only processing speed approached the level of significance with 47.5% of persons below norm. Findings suggest that persons with COPD have domain-specific cognitive deficits that are greater than those occurring in normal aging.

Keywords: Domain-specific cognitive decline, COPD

CHAPTER I

Background and Significance

COPD is a major public health problem. Persons with COPD have a 10-fold higher risk of developing disability than members of the general population (Eisner et al., 2011). Based on data from the 2007-2012 National Health and Nutrition Examination Survey (NHANES), a nationally representative data set in the United States (U.S.), 14.7% of adults in the U.S. aged 40 - 79 had measurable airflow obstruction; 9.4% had mild obstruction and 5.3% had moderate to severe obstruction (Tilert, Paulose-Ram, & Brody, 2015). In another nationally representative survey, the Health and Retirement Study (HRS), in persons over the age of 50 with COPD there is an 8.6% decreased likelihood of being employed, a 3.9% increase in the probability of collecting Social Security Disability Insurance and 1.7% increase in the use of Supplement Security Income (Snider et al., 2012). COPD is a public health burden as it leads to disability which interferes with the ability to work.

Beyond the changes that occur in the pulmonary system, COPD has extrapulmonary effects which add to the risk of disability. One extrapulmonary effect is a change in muscles which includes a shift in fiber type, weakening of the quadriceps, and atrophy (Bone, Hepgul, Kon, & Maddocks, 2017). When the loss of skeletal muscle is associated with a decline in physical function it is known as sarcopenia which offers prognostic information in COPD independent of pulmonary function (Bone et al., 2017). The prevalence of sarcopenia occurring in persons with COPD has been reported as 14.5% (95% CI [11.8% to 17.4%]), (Jones et al., 2015).

Another extrapulmonary effect of COPD is a change in cognition. It is generally recognized that there is a high prevalence of cognitive decline. However, there are inconsistencies in the evidence related to the prevalence. Cognitive decline has been reported in 22% - 77% of patients with COPD (Ambrosino, Bruletti, Scala, Porta, & Vitacca, 2002; Grant, Heaton, McSweeny, Adams, & Timms, 1982; Heaton, Grant, McSweeny, Adams, & Petty, 1983). The wide variation in the estimated prevalence of cognitive decline may be attributed to the selection of neuropsychological measures and inclusion criteria such disease severity. In most studies that used global measures of cognition, it was suggested from the findings that between groups there was no significant difference to a significant difference cognition prevalent in 5.5% of persons with COPD (Incalzi et al., 2002; Isoaho, Puolijoki, Huhti, Laippala, & Kivela, 1996; Stuss, Peterkin, Guzman, Guzman, & Troyer, 1977, Thakur et al., 2010). In contrast, when using a neuropsychological battery, 48.5% - 77% of persons with hypoxemic COPD had cognitive decline in all abilities but the magnitude was not equal across all domains of cognition (Cleutjens et al., 2017; Grant et al., 1982; Incalzi et al., 1993). Several studies (Grant et al., 1982; Krop, Block, & Cohen, 1973; Prigatano, Parson, Lein, Wright & Hawryluk, 1983) found the prevalence of cognitive decline dramatically increases with worsening hypoxemia and hypercapnia. Independent of hypoxemia and disease severity, in the domain of processing speed, 57% of persons with acute exacerbation of COPD were in the impaired range and 20% were considered to have suffered pathological loss in processing speed (Dodd, Charlton, van den Broek, & Jones, 2013). These results indicate that the selection of neuropsychological measures, disease severity and exacerbations may partially explain the variation in estimated prevalence of cognitive decline.

Persons with COPD have a higher prevalence and are at a greater risk for developing mild cognitive impairment (MCI) than in controls. Mild cognitive impairment refers to a complaint of defective memory, normal activities of daily living, normal general cognitive function, abnormal memory function for age and absence of dementia (Petersen et al., 1997). Mild cognitive impairment was present is 36% of persons with COPD compared to 12% in controls (Villeneuve et al., 2012). COPD was associated with a substantive risk of global cognitive decline compared to referent subjects (OR 2.43; 95% CI [1.043 - 6.64]) (Thakur et al., 2010). A dose response was also noted with the risk of developing cognitive decline such that persons with COPD duration of 5 years or longer at baseline had the greatest risk of both MCI (HR 1.58, 95% CI [1.04 - 2.40]) and non-amnesic-MCI (HR 2.58, 95% CI [1.32–5.06]) (Singh et al., 2014). These results support persons with COPD have a higher prevalence and a greater risk for developing MCI than controls.

This dissertation includes a) a meta-analysis summarizing the effect size of domain-specific cognitive decline, b) a secondary analysis of the HRS data set to examine longitudinal changes in cognition, comparing people with and without COPD, and c) a pilot study examining feasibility and acceptability of the use of the National Institute of Health (NIH) toolbox in persons with COPD and describe a preliminary relationship between domain-specific cognition, functional performance and life satisfaction. This chapter describes the background for this work with an emphasis on the impact of COPD on domain-specific cognition. Brief descriptions of current biological theories of causes for changes in cognition that occurs in COPD are examined and a preliminary exploration of the relationship between domain-specific cognition, functional performance and life satisfaction are presented.

Cognitive function consists of the complex processes by which an individual perceives, registers, stores, retrieves, and uses information from the environment to adapt behavior to new situations (Dodd, Getov, & Jones, 2010). To provide more information about the nature of cognitive function, cognitive processes have been separated into discrete domains. According to Dodd et al., (2010, p.914), no universal classification or division of cognitive domains has been accepted. It is important to note that even though cognition is reported in specific domains, it is difficult to examine a domain in isolation as domains are part of the process of cognition and many occur at the same time. Presently, there is not a standard assessment tool to assess global cognition and there is no standard for the types or number of neuropsychological tests required for evaluation of cognitive domains.

The prevalence and extent of domain-specific cognitive decline in COPD has poorly studied. In a systematic review to determine the prevalence of cognitive impairment in persons with COPD, a classification system of cognitive domains proposed by Lezak (2004 as cited in Torres-Sanchez et al., 2015) which included the domains: perception, attention, memory and learning, executive function and language. Prevalence was of cognitive decline was found in all domains. However, extent of cognitive decline was not examined. Another frequently studied cognitive domain is processing speed. Processing speed is an underlying cognitive process that is associated with several cognitive processes. These six domains will be examined in this research.

Cognitive Domains

Perception

Little is known about the effect of COPD on the cognitive domain of perception. Perception is the processes and activities in which one extracts stimuli and information from

the environment and acts upon it (Torres-Sanchez et al., 2015). To perceive, one must be able to attend to the stimuli. Thus, perception and attention, even though they are separate areas of cognition, are often tested together. Several studies have examined the cognitive domain of perception (Antonelli-Incalzi et al., 2008; Grant et al., 1982; Orth et al., 2008; Prigatano et al., 1983; Villeneuve et al., 2012). The results were mixed. The studies used a variety of measures making comparison between studies difficult. To understand the effect of COPD on perception, further research is needed.

Attention

Extensive research has been done of the relationship COPD and attention. Attention is a major contributor to cognitive performance as it is a process of selection and reduction of relevant aspects (Orth et al., 2008). Although several studies have examined the relationship between COPD and attention (Favalli, Miozzo, Cossi, & Marengoni, 2008; Grant et al., 1982; Klein, Gauggel, Sachs, &Pohl, 2010; Liesker et al., 2004; Parekh, et al. 2005; Pereira et al., 2011; Vos, Folgering, & van Herwaarden et al., 1995), these studies have used different neuropsychological tests yielding mixed results. These majority of the findings suggest that persons with COPD may experience cognitive impairment in the domain of attention.

Memory and Learning

People with COPD had poorer performance on tests of memory and learning. One way to categorize memory and learning are short-term and long-term memory. Short-term memory is also called immediate recall. Long-term memory is also called delayed recall or learning. A multitude of tests have been used to compare memory in persons with COPD and controls. The results were mixed. On tests of short-term memory, when tested with digit span forward, no significant difference was found between the groups (Cleutjens et al., 2014;

Incalzi et al., 1993; Kozora, Filley, Julian, & Cullum, 1999; Ortapamuk & Naldoken, 2006; Pereira et al., 2011; Zhang et al., 2013). It has been found that persons with COPD had poorer cognitive function in both verbal immediate and delayed recall (Dodd et al., 2013; Favalli et al., 2008; Grant et al., 1982; Hjalmarsen et al., 1999; Incalzi et al., 1993; Incalzi et al., 1997; Kozora et al., 1999; Ortapamuk & Naldoken, 2006; Pereira et al., 2011; & Zhou et al., 2012). One explanation for these differences in results is a model of working memory that is fractioned into a central controlling system aided by two peripheral systems. The central executive system forms strategies to retrieve information for the two slave systems: the phonological loop (digit span forward) and the visuospatial sketch pad (speech-based material) (Strauss, Sherman & Spreen, 2005). These findings support that persons with COPD have more problems with speech-based material in the domain of memory and learning than controls.

Executive Function

COPD does not impact the processes that make up executive function equally. Executive function is the cognitive processes necessary for planning, organizing, focusing attention, problem solving, remembering instructions, and juggling multiple tasks successfully (Torres-Sanchez et al., 2015). Several neuropsychological tests have been used to test executive function. One test used to assess executive function is verbal fluency. The results of this test are mixed. Several studies reported significant difference (Dodd et al., 2013; Incalzi et al., 1993; Prigatano et al., 1983; Zhou et al., 2012) while others found no significant differences on tests of language (Favalli et al., 2008: Grant et al., 1982; Kozora et al., 2005; Kozora, Emery, Zhang, & Make, 2010; Ortapamuk et al., 2006; Pereira et al., 2011). One study reported performance of persons with COPD on verbal fluency test had

statistically significantly lower scores than controls, but the deficit did not reach the clinically impaired range (Kozora et al., 1999). One important factor that the study brought to attention is that although many studies have found statistically significant declines in domain-specific cognition, the clinical relevance of these declines remain unknown.

Another test frequently used to assess executive function is TMT-B. Persons with COPD were found to have poorer performance than aged matched control (Bratek et al., 2015; Dal Ben & Bricolo, 2012; Favalli et al., 2008; Liesker et al., 2004; Park & Larson, 2015). In one study (Dal Negro, Bonadiman, Tognella, Bricolog, & Turco, 2014), the cognitive deterioration in executive function observed in respiratory patients aged 40-69 years was equivalent to the cognitive deterioration reported in healthy subject aged 70-79 years. Cognitive decline in the domain of executive function may begin in the early stages of COPD. Further research is needed to understand the relationship between executive function and its impact on performing daily activities.

Language

Language is impacted by COPD but may not be as affected as other cognitive domains. Results are inconsistent on test of language. When language was assessed using the aphasia screening test the results found no significance differences between those with COPD and controls (Grant et al., 1982). In contrast, Prigatano et al. (1983), found a significant difference between the two groups using same measure. When language ability was tested using the Boston Naming test, no significant difference was found between persons with COPD and controls (Kozora et al, 1999; Kozora et al. 2005; Kozora et al., 2010). These studies provide some evidence that not all domains are affected to the same extent.

Processing Speed

Persons with COPD have a slower processing speed than age matched controls. Processing speed is the ability to fluently perform relatively easy cognitive tasks and the flexibility to move rapidly from one task to another. Studies have consistently found that persons with COPD have slower overall processing speed regardless of the neuropsychological test used to assess processing speed (Grant et al., 1982; Klein et al, 2010; Liesker et al., 2004; Orth et al., 2008; Vos et al., 1995). The loss of cognitive flexibility is a consistent finding in persons with COPD and clinical implications need to be examined.

Mechanisms of Cognitive Decline in COPD

Multiple pathophysiological mechanisms have been examined as possible causes of cognitive decline in persons with COPD. Possible mechanisms include hypoxemia, hypercapnia, cerebral metabolic abnormalities, changes in cerebral perfusion, inflammatory processes, changes in brain structures and exacerbations. The impact that each of these mechanisms has on domain-specific cognition will be briefly discussed**.**

Hypoxemia

There is a strong negative association between hypoxemia and cognitive decline. In a study modeling impact of COPD on the brain, pathways linking disease severity with impaired cognitive performance were mediate through oxygen dependence (Borson et al. 2008). The rate of cognitive impairment increased from 27% in individuals with mild hypoxemia to 61% in individuals with severe hypoxemia (Grant et al., 1987). As hypoxemia increased persons with COPD scored progressively worse on the Halstead Battery Index (control 0.59(0.26), mildly hypoxic 0.65 (0.23), moderately hypoxic 0.73 (0.24), and severely hypoxic 0.77 (0.23)). Persons with moderate and severe hypoxia were statistically indistinguishable from each other. These

results support the negative relationship between hypoxemia and cognitive decline. Long-term oxygen therapy may prevent COPD hypoxemia-induced cognitive decline has been investigated. Persons with hypoxemic COPD that were prescribed and used long-term oxygen therapy had significantly less impairment in the domains of global cognition, executive function and attention compared to those that did not use oxygen or used it on an as needed basis (Dal Negro, Bonadiman, Bricolo, Tognella, & Turco, 2015, Karamanli, Ilik, Kayhan, & Pazarli, 2015). In domains of processing speed, ability to detect correct sequence of tones and serial memory, was not improved by providing short term oxygen therapy did not reverse information processing deficits in hypoxemic COPD (Wilson, Kaplan, Timms, & Dawson, 1985). These results provide support that hypoxemia-induced cognitive decline may be slowed or prevented with the use of long-term oxygen therapy but not short-term oxygen therapy.

Hypercapnia

The relationship between hypercapnia and cognitive decline in persons with COPD is not clear. Increased carbon dioxide in the blood can lead to an increase in free radical formation and oxygen dependent enzymes which can result in global neuronal injury (Cleutjens et al., 2014). In the Nocturnal Oxygen Therapy Trial (NOTT) found no correlations between any domains of cognitive function and hypercapnia (Grant et al., 1987). In contrast, the level of $PaCO_2$ was negatively correlated with scores of executive functions (Parekh et al., 2005), verbal memory (Incalzi et al., 1997) and attention and processing speed (Incalzi et al., 1993). Further research is needed to understand the impact of hypercapnia on cognitive domains in COPD.

Cerebral metabolites

Cerebral metabolic abnormalities have been implicated as a possible cause for the change in cognition that occurs with COPD. In a preliminary study, cerebral metabolites (N-

acetyl aspartate, creatine, choline and myo-inositol) and the neuropsychological tests were significantly lower in persons with COPD (Shim et al., 2001). In examining relationships of these metabolites, only the decrease in choline in the parietal white matter was associated with the general memory quotient of the Wechsler memory scale (Shim et al., 2001). There is some evidence that select cerebral metabolites are associated with negative cognitive changes in the domain of memory and learning in persons with COPD. However, the clinical significance of cerebral metabolic changes and their role in cognitive impairment in COPD requires further investigation.

Cerebral perfusion

Change in cerebral perfusion patterns is another possible mechanism that may lead to cognitive impairment in persons with COPD. There is strong evidence that changes in patterns of cerebral perfusion in persons with COPD are associated with cognitive impairment. In a study comparing cerebral perfusion patterns in patients with COPD and normal age-related perfusion changes, there was a downward trend in cerebral perfusion in most regions of interest which had a direct negative effect on the performance of neuropsychological tests for verbal attainment, attention, and deductive reasoning (Antonelli-Incalzi et al., 2003) and verbal memory, attention and delayed recall (Ortapamuk & Naldoken, 2006). These findings support that in COPD there is decrease in cerebral perfusion and subsequent domain-specific cognitive impairment.

Chronic inflammation

Since COPD is a disease of chronic inflammation, many studies have examined the relationship between COPD and circulating biomarkers of inflammation. There is weak evidence to support the role of chronic inflammation as a mechanism for cognitive decline in persons with COPD. In a pilot study, Borson et al. (2008) examined the relationship between

disease severity, cognitive measures, depression, anxiety, plasma measures of proinflammatory cytokine panel, and brain structures in persons with COPD. Statistically significant differences were found between controls and persons with COPD in global cognition, memory, mood and systemic inflammation marker TNFRI levels but not in brain structures (Borson et al., 2008). Another biomarker of inflammation that has been studied in persons with COPD is fibrinogen. Fibrinogen was associated with a significant faster four-year decline in general cognition independent of major vascular comorbidity (Rafnsson et al., 2007). These findings suggest that some biomarkers of inflammation associated with COPD may play a role in the development of cognitive impairment. More research is needed to develop a full understanding of chronic inflammation and its biomarkers in domain-specific cognitive decline in person with COPD.

Changes in brain structures

There are changes in neurophysiological architecture of the brain in persons with COPD that may impact cognitive function. There is a strong association between COPD, hypoxemia as measured by arterial blood gases and changes in brain structures leading to cortical atrophy. Stuss et al. (1997) compared CT scans and neuropsychological tests of persons with mild and severe hypoxemic COPD. In the mildly hypoxemic group, the scan showed no cortical atrophy. In the severely hypoxemic group, cortical atrophy ranged from mild to severe and was associated with a decrease in performance on tests of memory and sustained attention (Stuss et al, 1997). Gray matter density was positively correlated with arterial blood PaO2 and negatively correlated with disease duration and poorer performance on two aspects of the MMSE; figure memory and visual reproduction (Zhang et al., 2013). In another study of gray matter, a reduction in white matter and a disturbance in functional activation of gray matter was found throughout the brain

with a subsequent negative change in global cognition (Dodd, Chung, van den Broek, Charlton, & Jones., 2012). Similarly, Borson et al. (2008) found a negative association with indicators of brain tissue damage (increased frontal choline), which in turn was associated with subcortical white matter attenuation. These studies provide evidence there are changes in neuorphysiological architecture of the brain and associated declines on various tests of cognition.

Exacerbations

In COPD, an exacerbation is an acute onset of sustained worsening of the person's symptoms of breathlessness, cough, increased sputum production and change in sputum that are beyond their normal day-to-day variation and poorer cognitive function has been associated with exacerbations. Dodd et al. (2013) compared patients with COPD exacerbations, patient with stable COPD, controls and normal values of age on multiple neuropsychological tests. The patients that experienced COPD exacerbation had poorer performance on all cognitive measures compared to stable COPD and controls. In processing speed, 57% were impaired and 20% had pathological deficits. Three months after exacerbation, a marginal recovery was found only in immediate recall and processing speed. Subsequently, COPD patients hospitalized for exacerbations are discharged home with unrecognized mild to severe cognitive impairment (Dodd et al., 2013). The findings have important implications in caring for persons during the recovery period after an exacerbation of COPD.

Domain-Specific Cognition, Functional Performance and Life Satisfaction

To depict the relationships between domain-specific cognition, functional performance, and life satisfaction a visual representation of Cognition, Functional Performance, and Life Satisfaction was created (see Figure 1 Visual Representation of Relationships among Domain-specific Cognition, Functional Performance and Life Satisfaction). This research was guided by

two frameworks: Revised Cleary & Wilson Model of Health-Related Quality of Life (Ferrans et al., 2005) and the Functional Status Framework (Leidy, 1994) (see Appendix A for more information see Figure A. 1 Revised Wilson and Cleary Model for Health-Related Quality to Life). The revised Wilson and Cleary Model for Health-Related Quality to Life illustrates the dynamic interactions between health, functioning, and life satisfaction (Ferrans et al., 2005). The Functional Status Framework defines functional performance as "those activities that people do in the normal course of their lives to meet basic needs and fulfill usual roles and maintain health and well-being" (Leidy, 1994, p. 198). Factors that may be related to functional performance include cognition, disease severity and symptoms, emotional states of anxiety and depression and sleep disruption (Leidy, 1994). Life satisfaction is subjective well-being related to how happy or satisfied someone is with important aspects of their life in the domains of health and functioning, psychological and spiritual, family, social and economic (Ferrans et al., 2005). This research will examine relationships among domain-specific cognition, functional performance and life satisfaction. Strong evidence suggests a difference in performance on measures of domain-specific cognition between persons with COPD and controls. There is evidence that domain-specific cognition and functional performance are impacted by the related factors of disease severity, symptoms of disease, emotional state and sleep disturbance. In respect to the impact of the psychosocial variables on domain-specific cognition little is known. Also, according to this model, cognition influences directly influence life satisfaction or is mediated by functional performance.

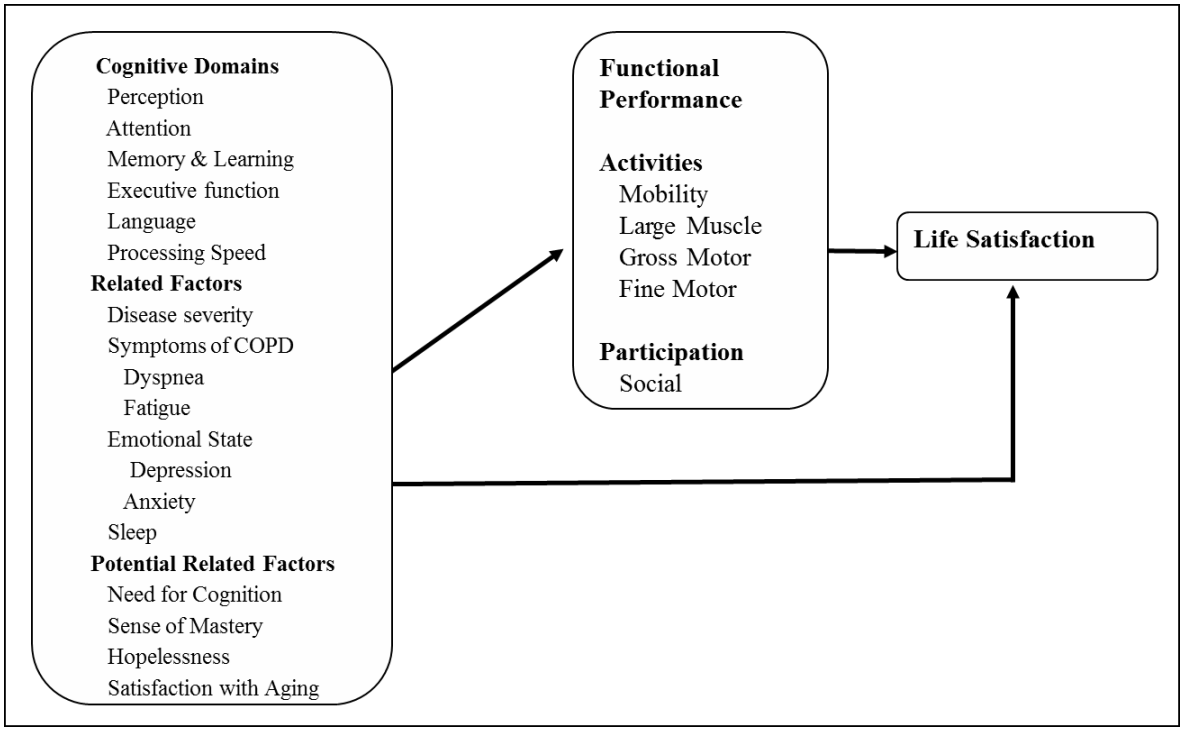


Figure 1: Visual Representation of Relationships among Domain-Specific Cognition, Functional Performance and Life Satisfaction

Disease Severity, Cognition, and Functional Performance Disease Severity

Disease Severity

The Global Initiative for Chronic Obstructive Lung Disease (GOLD COPD) staging system incorporates two staging systems. COPD is staged by using forced expiratory volume in one minute (FEV_1) % predicted. The FEV_1 is reported as the percentage of predicted normal value for age, sex height, and ethnicity. The stages are ranked 1-4 with 4 representing the poorest pulmonary function (for more information see Appendix B: Table 10 B. 1 GOLD COPD Staging System).

The GOLD COLD staging systems has a combined assessment which adds risks of exacerbation and symptoms to the classification system. Exacerbations are assessed by examining the numbers of exacerbations per year and determining whether the exacerbation led to hospitalization. Degrees of symptoms are determined by using the COPD Assessment

Test (for more information see Appendix C; COPD Assessment Test) and the modified Medical Research Council (mMRC) dyspnea scale (for more information see Appendix D; mMRC dyspnea scale). The results are then calculated using the combined assessment tool (for more information see Appendix E: Table 11 E. 1: Combined Assessment Tool of COPD).

Disease severity has been linked to a decline in both cognition and functional performance, but little is known about the relationship between the effect of cognitive decline on functional performance in persons with COPD. Disease severity is negatively correlated with cognition but is not equal across all domains. Persons with COPD scored significantly worse than healthy controls on three cognitive measures: attention, mental flexibility and cognition in routine operations (addition and subtraction) and those with lower $FEV_1 < 50\%$ score significantly worse that those with higher FEV_1on measures of attention (Liesker et al., 2004). Development of functional limitation has also been associated with measures of disease severity. For every one-liter decrement in FEV_1 or with every 5% decrease in oxygen saturation there was an increased risk of developing functional limitation (Eisner et al., 2011). These results suggest that as COPD progresses, cognition declines and there is a decrease in functional performance with increased disease severity.

There is some evidence to suggest that there is an association between cognitive decline and a decrease in functional performance in persons with COPD. Several studies found that persons with COPD that had lower scores on tests of global cognitive functioning also had greater prevalence of functional deficits in IADLs, ADLs and scores on the physical self-maintenance scale (Antonelli-Incalzi et al., 2008; Feng, Lim, Collinson, Ng, 2012; Ozge, Ozge, & Unal, 2006). In a prospective clinical study, in patients with COPD, persons with global cognitive decline also had declines in functional performance; 64.8% showed

global cognitive deficits with 22.2 % of those having difficulties in IADLs and 20.3% having difficulties in ADLs (Ozge, Ozge, & Unal, 2006). Antonelli-Incalzi et al. (2008) found as cognitive decline increased persons had a greater prevalence in dependence on ADLs and IADLs. In studying cognitive impairment and decreasing functional performance, moderate to severe airway obstruction was positively associated with cognitive IADLs disabilities (using the telephone, taking medications, and managing money) (Feng et al., 2012). In a two-year longitudinal study, the risk of developing disability or dependency in one or more ADLs for persons with COPD and MCI was greater than having COPD or MCI alone (Martinez, Richardson, Han & Cigolle, 2014). These results demonstrate that disease severity has a negative impact on both cognitive and functional performance. Additionally, there is greater risk of functional dependency if a person with COPD develops MCI but what remains unknown is if certain domains of cognition have a greater impact on developing the risk for decline in functional performance. Further research is needed to provide a better understanding of these relationships.

Symptoms

Dyspnea. Dyspnea is the subjective experience of breathlessness. Dyspnea is a "common and often progressively debilitating symptom in advanced chronic disease that is associated with fear, anxiety, activity limitations, and profound suffering" (Mularski et al., 2013). It is the most frequently reported respiratory symptom in COPD (Miravitlles, Anzueto, Legnani, Forstmeier, Fargel, 2007; Calverley, 2008). Due to its simplicity, ease of use and established validation, the most commonly used measure of dyspnea is the mMRC Dyspnea Scale (Okutan, Tas, Demirer & Kartaloglu, 2013). Dyspnea is the usual reason for seeking medical attention**,** chief contributor to disability, limiting factor for exercise, precipitates hospitalization and it has a

negative impact on functional performance, health-related quality of life and it is independent marker for premature death (Leidy et al., 2014; Okutan et al., 2013; Rabe et al., 2007; Ries, 2006; Viegi et al., 2007). These studies support that dyspnea impacts both functional performance and life satisfaction.

Fatigue. Fatigue is a major problem for persons with COPD. Fatigue is a "subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with the individuals' ability to function to their normal capacity" (Ream & Richardson, 1996). In persons with COPD, fatigue is the most common reported non-respiratory symptom and is worse in the afternoon (Antoniu, Petrescu, Stanescu, Anisie, & Boiculese, 2015; Antoniu & Ungureanu, 2015; Kapella, Larson, Patel, Covey, & Berry, 2006; Stridsman , Lindberg & Skar, 2014). In persons with COPD, fatigue is associated with poorer general health, anxious and depressed moods, decreased sleep quality, impaired concentration, decline in functional performance, decrease in daily hobbies and pastime activities, lower level of social functioning, limited relationships with family and friends, lack of motivation, less enjoyment in personal life and feelings of helplessness (Antoniu & Ungureanu, 2015; Antoniu, et al., 2015; Breslin et al. 1998; Kapella et al., 2006; Stridsman et al., 2014). These results support that the fatigue impacts domain-specific cognition, functional performance and life satisfaction.

Emotional State

Depression. There is a high prevalence of depression in persons with COPD. The prevalence of depression in persons with COPD ranges from 10% - 57% (Pumar et al., 2014). Depression in persons with COPD is associated with increased symptom burden which impacts functional performance. Persons with COPD and depression walked a shorter distance in the 6-

min walk test, showed less physical activity, increased difficulty in performing daily activities, poorer physical and social functioning and a worse quality of life (Borges-Santos et al., 2015; Pumar et al., 2014; Rivera et al., 2016). It is important to consider the many clinical implications of depression.

Anxiety. There is a higher rate of anxiety in persons with COPD than controls. The prevalence rate of anxiety ranges between 7% - 50% (Pumar et al., 2014). Anxiety is a subjective state defined as an unpleasant emotional arousal, characterized by feelings of tension and apprehension and heightened autonomic nervous system (Giardino et al., 2010). The most common anxiety disorders in persons with COPD are generalized anxiety and panic attacks which occur in approximately one-third of persons with COPD. In persons with COPD, a ten-point increase in anxiety score was significantly associated with a mean decrease in the 6-minute walk distance of nine meters and a one Watt decrease in peak exercise workload indicating a decrease in functional capacity, and a two-point increase in St. George Respiratory Questionnaire and Shortness of Breath Questionnaire indicating a decrease in quality of life and increase in shortness of breath (Giardino et al., 2010). It has been documented that anxiety impacts functional performance and quality of life, but further research needed to determine how it impacts domain-specific cognition in a person with COPD.

Sleep

Sleep disturbances are common in persons with COPD and are negatively associated with cognition. In persons with COPD, the prevalence of self-reported sleep disturbance is 24% (Omachi et al., 2012). The impact of self-reported sleep disturbance on the domains of cognition has mixed results. Disturbed sleep was associated with worse learning and episodic memory scores but not with tests of executive function (Omachi et al., 2012). In

contrast, subjective sleep quality was associated with slower reaction time and poorer executive function but not memory (Biddle et al., 2017). The mixed results from the impact of subjective sleep disturbances on cognition indicate further research needs to be done to understand the relationship between sleep and cognitive decline in persons with COPD.

Psychosocial factors

Need for cognition. One's perception of the need for cognition may impact behaviors that in turn domain-specific cognition. The need for cognition is "the tendency for an individual to engage in and enjoy thinking" (Cacioppo, Petty, & Kao, 1984). Engaging in cognitive activities may enhance cognitive capacity. No studies were found that examined the need for cognition in the person with COPD.

Sense of Mastery. The sense of mastery has been associated with better cognitive performance. It has been defined as the extent that one believes that they have the power to control life chances including outcomes (Clench-Aas, Nes, & Aaro, 2017). Individuals with a higher sense of mastery trust that they can adapt their behaviors in each circumstance to achieve their goal while those with a low sense of mastery feel powerless. The sense of mastery is not considered a stable element of personality, but a personal resource that constitutes a crucial coping skill that is important to daily functioning, health and well-being. It evolves and changes over the lifespan in response to experiences and circumstances (Clench-Aas et al., 2017). Higher levels of mastery have been associated with better health, more health promoting behaviors, better performance on tests of memory and cognitive function (Colcombe & Kramer, 2003). Old age, low socioeconomic status, and poor health are inversely associated with feelings of mastery (Schieman & Turner, 1998). Additionally, the experiences of growing old and losing personal resources may be more burdensome and likely to erode sense of mastery (Schieman & Turner,

1998). No studies were found that examined the relationship between sense of mastery and COPD.

Hopelessness. A person's level of hopelessness can be determined by defining hopelessness in terms of a system of negative expectances concerning himself and his future life (Beck & Weissman, 1974). A lack of hope, or "giving up," is generally believed to have a negative impact on physical health and psychological well-being; more negative emotions, are more vulnerable to depression, and have higher levels of anxiety (Satici & Uysal, 2017). No studies were found that examined the relationship between hopelessness and COPD.

Satisfaction with Aging. Satisfaction with aging is a psychosocial predictor of disabilities. According to Levy, Slade and Kasl (2002) satisfaction with aging is defined as one's self-perception of aging or an individual's beliefs about their own aging. Attitudes towards aging develop over one's lifetime. They are derived from encounters with the elderly and societal attitudes towards aging. When these attitudes are internalized, they become part of one's self and the expectations for the trajectory of one's own aging process. When one reaches late adulthood the positive or negative expectations that are internalized regarding aging are likely to be experienced impacting both cognitive and physical functioning (Levy et al., 2002). No studies were found that examined the relationship between satisfaction with aging and COPD.

Functional performance in persons with COPD

COPD is characterized by gradual deterioration in functional performance. Higher rates of disability in instrumental activities of daily living, activities of daily living and mobility disabilities were found in persons with COPD compared to the general population (Rodriguez-Rodriguez et al., 2013). Strategies used to compensate for the reduction in functional performance included planning, pacing and prioritizing for activities of daily living and various

disease management activities (Cicutto, Brooks, & Henderson, 2004). Further research of the relationship between changes in domain-specific cognition and functional performance is needed to determine which ADLs and IADLs are most impacted by the decline in cognition.

Life Satisfaction

COPD is characterized by gradual deterioration in functional performance. Higher rates of disability in instrumental activities of daily living, activities of daily living and mobility disabilities were found in persons with COPD compared to the general population (Rodriguez-Rodriguez et al., 2013). Strategies used to compensate for the reduction in functional performance included planning, pacing and prioritizing for activities of daily living and various disease management activities (Cicutto, Brooks, & Henderson, 2004). Further research of the relationship between changes in domain-specific cognition and functional performance is needed to determine which ADLs and IADLs are most impacted by the decline in cognition. Life satisfaction is one of the most important indicators of quality of life (Ferrans & Powers, 1985). "Overall quality of life is the subjective well-being related to how happy or satisfied someone is with life as a whole" (Ferrans et al, 2005). It can be measured with a uniscale consisting of one question that states "Please rate your overall quality of life" or multiple-item scales assessing life satisfaction or happiness (Ferrans, 2007). Very few studies have examined life satisfaction in COPD, most of the studies focus on relationship between health-related quality of life and COPD. In comparisons of scores on life satisfaction, persons with COPD on long term oxygen therapy had significantly lower life satisfaction levels (Sturesson & Branholm, 2000). Comparing life satisfaction in persons with COPD to those with coronary artery disease, both groups reported moderate satisfaction with life, however, the group with coronary artery disease was significantly more

satisfied with life that persons with COPD (Brown, Rawlinson, & Hilles, 1981). These findings support there is a variance in life satisfaction scores in persons with COPD. Further research is needed to develop an understanding of the impact of domain-specific cognitive decline on life satisfaction persons with COPD.

Specific Aims

This dissertation will be completed by writing three papers that address the following aims:

Aim 1. Describe the state of the science in regard to patterns of decline in domain-specific cognitive impairment in persons with COPD.

It is hypothesized that the findings will support that cognitive impairment does not occur equally across all domains in persons with COPD and differs from cognitive changes that occur in normal aging.

Aim 2. Describe the relationship between disease severity and change in domain-specific cognitive function, functional performance and life satisfaction in persons with COPD.

It is hypothesized with greater the disease severity there will be poorer performance on tests of domain-specific cognition and functional performance and subsequently lower scores on life satisfaction

Sub-aim 1: Determine if the relationship between cognition and life satisfaction is mediated by functional performance.

It is hypothesized that the relationship between domain-specific cognition and life satisfaction is mediated by functional performance.

Sub-aim 2: Explore the relationship between the psychosocial variables of need for cognition, sense of mastery, satisfaction with aging and hopeless and their impact on cognition in persons with COPD.

It is hypothesized that each psychosocial variable will impact cognition.

Aim 3. Examine the feasibility and acceptability of the computer assisted testing using the NIH Toolbox Cognitive Battery and selected assessment tools from PROMIS® to describe a preliminary estimate of the strength of the relationship among domain-specific cognition, functional performance and life satisfaction in persons with mild to severe COPD.

The working hypothesis is that assessments delivered via tablet will be a feasible and well accepted by persons with COPD. The second hypothesis is that functional performance with be a mediating factor between domain-specific cognition and life satisfaction

BIBLIOGRAPHY

Ambrosino, N., Bruletti, G., Scala, V., Porta, R., & Vitacca, M. (2002). Cognitive and perceived health status in patient with chronic obstructive pulmonary disease surviving acute on chronic respiratory failure: a controlled study. *Intensive Care Medicine, 28*, 170-177. http://dx.doi.org/doi:10.1007s00134-1165-6

Ameringer, S., Elswick, R., Menzies, V., Robins, J., Starkweather, A., Walter, J., & Jallo, N. (2016). Psychometric Evaluation of the Patient-Reported Outcome Measurement Information System Fatigue-Short Form Across Diverse Populations. *Nursing Research, 65*(4), 279-289. http://dx.doi.org/10.1097/NNR.0000000000000162

Antonelli-Incalzi, R., Marra, C., Giordano, A., Calcagni, M., Cappa, A., Basso, S., . . . Fuso, L. (2003). Cognitive impairment in chronic obstructive pulmonary disease: A neuropsychological and spect study. *Journal of Neurology, 250*, 325-332. http://dx.doi.org10.1007/s00415-003-1005-4

Antonelli-Incalzi, R., Corsonello, A., Trojano, L., Acanfora, D., Spada, A., Izzo, O., & Rengo, F. (2008).
Correlation between cognitive impairment and dependence in hypoxemic COPD. *Journal of clinical and experimental neuropsychology, 30*(2), 141-150.

Antoniu, S., & Ungureanu, D. (2015). Measuring fatigue as a symptom in COPD: From descriptors and questionnaires to the importance of the problem. *Chronic Respiratory Disease, 12*(3), 179-188. http://dx.doi.org/10.1177/1479972315575716

Antoniu, S., Petrescu, E., Stanescu, R., Anisie, E., & Boiculese, L. (2015). Impact of fatigue in patient in patients with chronic obstructive pulmonary disease: results form an exploratory study.
Therapeutic Advances in Respiratory Disease, 22, 1-8.
http://dx.doi.org/10.1177/1753465815617707

Beck, A., & Weissman, A. (1974). THE MEASUREMENT OF PESSIMISM: THE HOPELESSNESS SCALE. *Journal of Consulting and Clinical Psychology, 42*(6), 861-865.

Biddle, D., Naismith, S., Griffiths, K., Christensen, H., Hickie, I., & Glozier, N. (2017). Associations of objective and subjective sleep disturbance with cognitive function in older men with comorbid depression and insomnia. *Sleep Health, 3*, 178-183. http://dx.doi.org/10.1016/j.sleh.2017.03.007

Bone, A., Hepgul, N., Kon, S., & Maddocks, M. (2017). Sarcopenia and frailty in chronic respiratory disease: Lessons from gerontology. *Chronic Respiratory Disease, 14*(1), 85-99. http://dx.doi.org/10.1177/1479972316679664

Borges-Santos, E., Wada, J., Marques da Silva, C., Silva, R., Stelmach, R., Carvalho, C., & Lunardi, A. (2015). Anxiety and depression are related to dyspnea and clinical control but not with thoracoabdominal mechanism in patients with COPD. *Respiratory Physiology & Neurobiology, 210*, 1-6. http://dx.doi.org/10.1016/j.resp.2015.01.011

Borson, S., Scanlan, J., Friedman, S., Zuhr, E., Fields, J., Aylward, E., . . . Yeh, S. (2008). Modeling the impact of COPD on the brain. *Int J Chron Obstruct Pulmon Dis, 3*(3), 429-434.

Bratek, A., Zawada, K., Beil-Gawelczyk, J., Beil, S., Sozanska, E., Krzysztof, K., . . . Pierzchala, W. (2015). Depressiveness, symptoms of anxiety and cognitive dysfunctions in patients with asthma and chronic obstructive pulmonary disease (COPD): possible associations with inflammation markers: a pilot study. *J Neural Transm, 22*(122 (suppl)), S83-S91. http://dx.doi.org./10.10007/s00702-014-1171-9

Breslin, E., van der Schan, C., Breukink, S., Meek, P., Mercer, K., Volz, W., & Louis, S. (1998). Perception of Fatigue and Quality of Life in Patients with COPD. *CHEST, 114*, 958-964.

Brown, J., Rawlinson, M., & Hilles, N. (1981). Life Satisfaction and Chronic Disease: Exploration of a Theoretical Model. *Medical Care, 19*(11), 1136-1146.

Cacioppo, J., Petty, R., & Kao, C. (1984). The efficient assessment of need for cognition. *J Pers Assess. 48*(3), 306-307. http://.dx.doi.org/ 10.1207/s15327752jpa4803_13

Calverley, P. (2008). Understanding Breathlessness in Mild Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory Critical Care Medicine, 177*, 564.

Cicutto, L., Brooks, D., & Henderson, K. (2004). Self-care issues from the perspective of individuals with chronic obstructive pulmonary disease. *Patient Educ Couns., 55*(168-176). http://dx.doi.org/10.1016/j.pec.2003.08.012

Clench-Aas, J., Nes, R., & Aaro, L. (2017). The perceived constraint subscale of the Sense of Mastery Scale: dimensionality and measurement invariance. *Qual Life Res, 26*, 127-138. http://dx.doi.org/10.1007/s11136-016-1359-6

Cleutjens, F. A., Spruit, M. A., Ponds, R. W., Dijkstra, J. B., Franssen, F. M., Wouters, E. F., & Janssen,D. J. (2014). Cognitive functioning in obstructive lung disease: results from the United Kingdom biobank. *J Am Med Dir Assoc, 15*(3), 214-219. http://dx.doi.org/10.1016/j.jamda.2013.12.007

Cleutjens, F. A., Franssen, F. M., Spruit, M. A., Vanfleteren, L., Gijsen, C., Dijkstra, J. B., . . . Janssen, D.J. (2017). Domain-specific cognitive impairment in patients with COPD and control subjects. *International Journal of Chronic Obstructive Pulmonary Disease, 12*, 1-11.http://dx.doi.org./10.2147/COPD.S119633

Colcombe, S., & Kramer, A. (2003). Fitness Effects on the Cognitive Function of Older Adults. *Psychological Science, 14*(2), 125-130.

Dal Ben, S., & Bricolo, F. P. (2012). The Psychological and Cognitive Profile. In R. W. Dal Negro & R. Hodder (Eds.), *Long-Term Oxygen Therapy: new insight and perspectives* Milan, Italia: Springer.

Dal Negro, R. W., Bonadiman, L., Tognella, S., Bricolo, F. P., & Turco, P. (2014). Extent and prevalence of cognitive dysfunction in chronic obstructive pulmonary disease, chronic non-obstructive bronchitis, and in asymptomatic smokers, compared to normal reference values. *Int J Chron Obstruct Pulmon Dis, 9*, 675-683. http://dx.doi.org/10.2147/COPD.S63485

Dal Negro, R. W., Bonadiman, L., Bricolo, F. P., Tognella, S., & Turco, P. (2015). Cognitive dysfunction in severe chronic obstructive pulmonary disease (COPD) with or without Long-Term Oxygen Therapy (LTOT). *Multidisciplinary Respiratory Medicine, 10*(1), 17. http://dx.doi.org/10.1186/1475-9276-5-10

Dodd, J. W., Getov, S. V., & Jones, P. W. (2010). Cognitive function in COPD. *Eur Respir J, 35*, 913- 922. http://dx.doi.org/10.1183/09031936.00125109

Dodd, J. W., Chung, A., van den Broek, M., Charlton, R., & Jones, P. W. (2012). Brain structure and function in chronic obstructive pulmonary disease: a multimodal cranial magnetic resonance imaging study. *American Journal respiratory critical care medicine, 186*(3), 240-245. http://dx.doi.org/10.1164/rccm.201202-0355OC

Dodd, J. W., Charlton, R., van den Broek, M., & Jones, P. W. (2013). Cognitive Dysfunction in Patients Hospitalized with Acute Exacerbation of COPD. *CHEST, 144*(1), 119-127.

Dodd, J. W., Novotny, P., Sciurba, F., Benzo, R., & Group, N. R. (2015). Executive Function, Survival and Hospitalization in Chronic Obstructive Pulmonary Disease. *Ann AM Thorac Soc, 12*(10). http://dx.doi.org/10.1513/AnnalsATS.201506-373)C

Eisner, M., Iribarren, C., Blanc, P., Yelin, E., Ackerson, L., Byl, N., . . . Katz, P. (2011). Development of disability in chronic obstructive pulmonary disease: beyond lung function. *Thorax, 66*, 108-114. http://dx.doi.org/10.1136/thx.2010.137661

Favalli, A., Miozzo, A., Cossi, S., & Marengoni, A. (2008). Differences in neuropsychological profile between healthy and COPD older persons. *Int J Geriatr Psychiatry, 23*(2), 220-221. http://dx.doi.org/10.1002/gps.1847

Feng, L., Lim, M. L., Collinson, S., & Ng, T. P. (2012). Pulmonary function and cognitive decline in an older Chinese population in Singapore. *COPD, 9*(5), 555-562. http://dx.doi.org/10.3109/15412555.2012.706341

Ferrans, C., & Powers, M. (1985). Quality of life index: development and psychometric properties *Advances in Nursing Science, 8*(1), 15-24Ferrans, C. (2007). Differences in What Quality-of-Life Instruments Measure. *Journal of the National Cancer Institute Monographs, 37*, 22-26.

Ferrans, C., Zerwic, J., Wilbur, J., & Larson, J. (2005). Conceptual Model of Health-Related Quality of Life. *Journal of Nursing Scholarship, 37*(4), 336-342.

Ferrans, C. (2007). Differences in What Quality-of-Life Instruments Measure. *Journal of the National Cancer Institute Monographs, 37*, 22-26.

Giardino, N., Curtis, J., Andrei, A., Fan, V., Benditt, J., Lyubkin, M., . . . Group, N. R. (2010). Anxiety is associated with diminished exercise performance and quality of life in sever emphysema: a cross- sectional study. *Respiratory Research, 11*(29), 11. http://dxdoi.org/10.1186/1465-9921-11-29

Grant, I., Heaton, R., McSweeny, J., Adams, K., & Timms, R. (1982). Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease. *Arh Intern Med, 142*, 1470-1476.

Grant, I., Prigatano, G., Heaton, R., McSweeny, A., Wright, E., & Adams, K. (1987). Progressive Neuropsychologic Impairment and Hypoxemia. *Arch Gen Psychiatry, 44*, 999-1006.

Heaton, R., Grant, I., McSweeny, J., Adams, K., & Petty, T. (1983). Psychologic Effects of Continuous and Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Pulmonary Disease. *Acrh Intern Med, 143*, 1941-1947.

Hjalmarsen, A., Waterloo, K., Dahl, A., Jorde, R., & Viitanen, M. (1999). Effect of Long-Term Oxygen Therapy on Cognitive Neurological Dysfunction in Chronic Obstructive Pulmonary Disease.
European Neurology, 42, 27-35.

Incalzi, R. A., Gemma, A., Marra, C., Muzzolon, R., Capparella, O., & Carbonin, P. (1993). Chronic Obstructive Pulmonary Disease: An Original Model of Cognitive Decline. *Am Re Respir Dis, 148*, 418-424.

Incalzi, R. A., Gemma, A., Marra, C., Capparella, O., Fuso, L., & Carbonin, P. (1997). Verbal Memory Impairment in COPD: Its Mechanisms and Clinical Relevance. *CHEST, 112*, 1506-1513.

Incalzi, R. A., Bellia, V., Maggi. S., Imperiale, C., Capparella, O., Catalano, R., Carbonin, P., Rengo, F., & the Sa.R.A. (Salute Respiratoria nell'Anziano) Study Group. (2002). Mild to moderate chronic airways disease does not carry an excess risk of cognitive dysfunction. *Aging Clin Exp Res, 14*(5), 395-401.

Isoaho, R., Puolijoki, H., Huhti, E., Laippala, P., & Kivela, S. (1996). Chronic Obstructive Pulmonary Disease and Cognitive Impairment in the Elderly *International Psychogeriatric, 8*(113-125).

Jones, S., Maddocks, M., Kon, S., Canavan, J., Nolan, C., Clark, A., ...Mam, W. (2105). Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. *Thorax. 70*(3). 213-218. http:dx.doi.org/10.1136/thoraxjnl-2014-206440

Kapella, M., Larson, J., Patel, M., Covey, M., & Berry, J. (2006). Subjective fatigue, influencing variables, and consequences in chronic obstructive pulmonary disease. *Nursing Research, 55*, 10- 17.

Kapella, M., Larson, J., Covey, M., & Alex, C. (2011). Functional Performance in Chronic Obstructive Pulmonary Disease Declines with Time. *Med Sci Sports Exerc, 43*(2), 2118-2224. http//dx.doi.org//10.1249/MSS.0b013e3181eb6024

Klein, M., Gauggel, S., Sachs, G., & Pohl, W. (2010). Impact of chronic obstructive pulmonary disease (COPD) on attention functions. *Respiratory Medicine, 104*, 52-60. http://dx.doi.org/10.1016/j.med.2009.08.008

Kozora, E., Filley, C., Julian, L., & Cullum, M. (1999). Cognitive Functioning in Patients with Chronic Obstructive Pulmonary Disease and Mild Hypoxemia Compared with Patients with Mild Alzheimer Disease and Normal Controls. *Neuropsychiatry, Neuropsychology and Behavioral Neurology. 12* (3). 178-181.

Kozora, E., Emery, C. F., Ellison, M., Wamboldt, F. S., Diaz, P. T., & Make, B. J. (2005). Improved Neurobehavioral Functioning in Emphysema Patients Following Lung Volume Reduction Surgery Compared to Medical Therapy. *CHEST, 128*, 2653-2663.

Kozora, E., Emery, C. F., Zhang, L., & Make, B. (2010). Improved Neurobehavioral Functioning in Emphysema Patients Following Medical Therapy. *Journal of Cardiopulmonary Rehabilitation and Prevention, 30*, 251-259.

Krop, H., Block, J., & Cohen, E. (1973). Neuropsychologic Effects of Continuous Oxygen Therapy in Chronic Obstructive Pulmonary Disease*. *CHEST, 64*(3), 318-322.

Leidy, N. (1994). Functional status and the forward progress of merry-go-rounds: toward a coherent analytical framework. *Nur Res, 43*(4), 196-202.

Leidy, N., Murray, L., Monz, B., Nelsen, L., Goldman, M., Jones, P. W., . . . Sethi, S. (2014). Measuring respiratory symptoms of COPD: performance of the EXACT-respiratory Tool (E-RS) in three clinical trials. *Respiratory Research, 15*(124), 1-10. http://respiratory-research.com/content/15/1/124

Levy, B., Slade, M., & Kasl, S. (2002). Longitudinal Benefit of Positive Self-Perceptions of Aging on Functional Health. *Psychological Science, 57B*(5), 409-417.

Levy, B., & Leifheit-Limson, E. (2009). The Stereotype-Matching Effect: Greater Influence on Functioning When Age Stereotypes Correspond to Outcomes. *Psychology and Aging, 24*(1), 230- 233. http://dx.doi.org/10.1037/a0014563

Liesker, J., Postma, D., Beukema, R., ten Hacken, N., van der Molen, T., Riemersma, R., van, Zomeren, E., & Kerstjens, H. (2004). Cognitive performance in patients with COPD. *Respiratory Medicine, 98*, 351-356. http://dx.doi.org/10.1016/j.med.2003.1.004

Martinez, C., Richardson, C., Han, M., & Cigolle, C. (2014). Chronic Obstructive Pulmonary Disease, Cognitive Impairment and Development of Disability: The Health Retirement Study. *AnnalsATS, 11*(9), 1362-1370. http://dx.doi.org/10.1513/AnnalsATS.20145-187OC

Miravitlles, M., Anzueto, A., Legnani, D., Forstmeier, L., & Fargel, M. (2007). Patient's perception of exacerbations of COPD – the PERCEIVE study. *Respiratory Medicine, 101*, 453-460. http://dx.doi.org/10.1010/j.rmed.2006.07.010

Mularski, R., Reinke, L., Carrieri-Kohlman, V., Fischer, M., Campbell, M., Rocker, G., . . . White, D. (2013). An Official American Thoracic Society, Workshop Report: Assessment and Palliative Management of Dyspnea Crisis. *Annals ATS, 10*(5), S98-106. http://dx.doi.org/10.1513/AnnalsATS.201306-169ST

Okutan, O., Tas, D., Dermirer, E., & Kartaloglu, Z. (2013). Evaluation of Quality of Life with the Chronic Obstructive Pulmonary Disease Assessment Test in Chronic Obstructive Pulmonary Disease and the Effect of Dyspnea on Disease-Specific Quality of Life in These Patients. *Yonssi Med J, 54*(5), 1214-1219. http://dx.doi.org/10.3349/ymj.2013.54.5.1214

Omachi, T., Blanc, P., Claman, D., Chen, H., Yelin, E., Julian, L., & Katz, P. (2012). Disturbed Sleep among COPD Patients is Longitudinally Associated with Mortality and Advers COPD Outcomes *Sleep Medicine, 13*(5), 476-483. http://dx.doi.org/10.1016/j.sleep.2011.12.007.

Ortapamuk, H., & Naldoken, S. (2006). Brain perfusion abnormalities in chronic obstructive pulmonary disease: comparison with cognitive impairment. *Annals of Nuclear Medicine, 20*(2), 99-106.

Orth, M., Diekmann, C., Suchan, B., Ducha, H., Widdig, W., Schultze-Werninghaus, G., . . . Kotterba, S. (2008). Driving Performance in patients with Chronic Obstructive Pulmonary Disease. *Journal of Physiology and Pharmacology, 59*(S6), 539-547.

Ozge, C., Ozge, A., & Unal, O. (2006). Cognitive and functional deterioration in patients with severe COPD. *Behavioural Neurology, 17*, 121-130.

Parekh, P., Blumenthal, J., Babyak, M., LaCaille, R., Rowe, S., Dancel, L., . . . Palmer, S. (2005). Gas Exchange and Exercise Capacity Affect Neurocognitive Performance in Patients with Lung Disease. *Psychosomatic Medicine, 67*, 425-432. http://dx.doi.org/10.1097/01.psy.0000160479.99765.18

Park, S., & Larson, J. (2015). Cognitive function as measured by trail making test in patients with COPD. *Western Journal of Nursing Research, 37*(2), 236-256. http://dx.doi.org/10.1177/0193945914530520

Pereira, E., Viana, C., Tauna, T., Sales, P., Lima, J., & Holanda, M. (2011). Improvement of Cognitive Function After a Three-Month Pulmonary Rehabilitation Program for COPD Patients. *Lung, 189*, 279-285. http://dx.doi.org./10.1007/s00408-011-9303-6

Petersen, R., Smith, G., Waring, S., Ivnik, R., Kokmen, E., & Tangelos, E. (1997). Aging, Memory, and Mild Cognitive Impairment. *International Psychogeriatrics, 9*(Suppl. 1), 65-69.

Prigatano, G. P., Parsons, O., Levin, D., Wright, E., & Hawryluk, G. (1983). Neuropsychological Test Performance in Mildly hypoxic Patients with Chronic Obstructive Pulmonary Disease. *Journal of Consultng and Clinical Psychology, 51*(1), 108-116.

Pumar, M., Gray, C., Walsh, J., Yang, I., Rolls, T., & Ward, D. (2014). Anxiety and depression - Important psychological comorbidities of COPD. *J Thorac Dix, 6*(11), 1615-1631. http://dx.doi.org/10.3978/j.issn.2072-1439.2014.09.28

Rafnsson, S., Deary, I., Smith, G., Whiteman, M., Rumley, A., Lowe, G., & Fowkes, G. (2007). Cognitive Decline and Markers of Inflammation and Homeostasis: The Edinburgh Artery Study.
Journal of the American Geriatrics Society, 55(5), 700-707.

Ream, E., & Richardson, A. (1996). Fatigue: a concept analysis. *Int J Nurs Stud, 33*(5), 519-529.

Rivera, C., Galicia, J., Navarrete, A., Garcia-Polo, C., Iturriaga, L., Herrejon, A., . . . Miravitlles, M. (2016). Factors Associated with Depression in COPD: A Multicenter Study. *Lung, 194*, 335-343. http://dx.doi.org/10.1007/s00408-016-9862-7

Rodríguez-Rodríguez, P., Jiménez –García, R., Hernández-Barrera, V., Carrasco-Garrido, P., Puente- Maestu, L., & Miguel-Díez, J. (2013). Prevalence of Physical Disability in Patients with Chronic Obstructive Pulmonary Disease and Associated Risk Factors. *COPD: Journal of Chronic Obstructive Pulmonary Disease, 10*(5), 611-617. http://dx.doi.org/10.3109/15412555.2013.781150

Satici, S., & Uysal, R. (2017). Psychologic al Vulnerability and Subjective Happiness: The Mediating Role of Hopelessness. *Stress and Health, 33*, 111-118. http://dx.doi.org10.1002/smi.2685

Schieman, S., & Turner, H. (1998). Age, disability, and the sense of mastery. *J Health Soc Beha 39*(3), 169-186.

Shim, T., Lee, J., Kim, S., Lim, T., Kim, S., Kim, D., & Kim, W. (2001). Cerebral Metabolic Abnormalities in COPD Patients Detected by Localized Proton Magnetic Resonance Spectroscopy. *CHEST, 120*, 1506-1513.

Singh, B., Mielke, M., Parsaik, A., Cha, R., Roberts, R., Scanion, P., . . . Peterson, R. (2014). A Prospective Study of Chronic Obstructive Pulmonary Disease and the Risk for Mild Cognitive Impairment. *JAMA Neurol, 71*(5), 581-588. http://dx.doi.org./10.001/jamaneurol.2014.94

Snider, J., Romley, J., Wong, K., Zhang, J., Eber, M., & Goldman, D. (2012). The Disability Burden of COPD. *COPD: Journal of Chronic Obstructive Pulmonary Disease, 9*(5), 513-521. http://dx.doi.org/10.3109/15412555.2012.696159

Strauss, E., Sherman, E., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests: ADMINISTRATION, NORMS and COMMENTARY*. New York, New York.: Oxford University Press.

Stridsman, C., Lindberg, A., & Skar, L. (2014). Fatigue in chronic obstructive pulmonary disease: a qualitative study of people's experiences. *Scandinavian Journal of Caring Science, 28*, 130. http://dx.doi.org/10.110/scs.12033

Sturesson, M., & Branholm, I. (2000). Life satisfaction in subjects with chronic obstructive pulmonary disease. *Work, 14*(2), 77-82.

Stuss, D., Peterkin, I., Guzman, D., Guzman, C., & Troyer, A. (1997). Chronic obstructive pulmonary disease: Effects of hypoxia on neurological and neuropsychological measures. *Journal of Clinical and Experimental Neruopsychology, 19*(4), 515-524. http://dx.doi.org/10.1080/01688639708403741

Thakur, N., Blanc, P., Julian L., Yelin, E., Katz, P, Sidney, S., Iribarren, C., & Eisner, M. (2010a). COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. *International Journal of Chronic Obstructive Pulmonary Disease, 5*, 263-269.

Tilert, T., Paulose-Ram, R., & Brody, D. (2015). Lung Obstruction Among Adults Aged 40–79: United States, 2007–2012 *NCHS Data Brief.* Retrieved from https://www.cdc.gov/nchs/data/databriefs/db180.pdf

Torres-Sanchez, I., Rodriquiez-Alzueta, E., Cabrera-Martos, I., Lopez-Torres, I., Moreno-Ramirez, M., & Valenze, M. (2015). Cognitive Impairment in COPD: a systematic review. *J Bras Pneumol, 41*(2), 182-190. http://dx.doi.org/10.1590/S1806-37132015000004424

Villeneuve, S., Pepin, V., Rahayel, S., Bertrand, J., Lorimier, M., Rizk, A., . . . Gagnon, J. (2012). Mild Cognitive Impairment in Moderate to Severe COPD: A Preliminary Study. *CHEST, 142*(6), 1516- 1526.

Vos, P., Folgering, H., & van Herwaarden, C. (1995). Visual attention in patients with chronic obstructive pulmonary disease. *Biological Psychology, 41*, 295-305.

Voyer, P., Champoux, N., Desrosiers, J., Landreville, P., Monette, J., Savoie, M., . . . Bedard, (2006). Assessment of inattention in the context of delirium screening: one size does not fit all! *International Psychogeriatrics, 28*(8), 1293-1301. http://dx.doi.org/10.1017S10416110216000533

Weintraub, S., Dikmen, S., Heaton, R., Tulsky, D., Zelzso, D., Slotkin, J., . . . Gershon, R. (2014). The Cognitive Battery of the NIH Toolbox for Assessment of Neurological and Behavioral Function: Validation in an Adult Sample. *Journal international Neuorphyshol Soc, 20*(6), 567-578. http://dx.doi.org/10.1017/S1355617714000320

Weissman, M., Sholomskas, D., Pottenger, M., Prusoff, B., & Locke, B. (1977). Assessing Depressive Symptoms in Five Psychiatric Populations: A Validation Study. *American Journal of Epidemiology, 106*(3), 203-214.

Wilson, D., Kaplan, R., Timms, R., & Dawson, M. (1985). Acute Effects of Oxygen Treatment Upon Information Processing in Hypoxemic COPD Patients. *CHEST, 88*(2), 239-243.

Zhang, H., Lin, W., Sun, Y., Huang, Y., Yang, T., Zheng, S., . . . Zhang, J. (2013). Reduced Regional Gray Matter Volume in Patients with Chronic Obstructive Pulmonary Disease: A Voxel-Based Morphometry Study. *AJNR Am J Neurordiol, 34*, 334-339. http://dx.doi.org./10.3174/ajnr.A3235

Zhou, G., Liu, J., Sun, F., Xin., X., Duan, L., Zhu, X., & Shi, Z. (2012). Association of Chronic Obstructive Pulmonary Disease with Cognitive Decline in Very Elderly Men. *Dementia and Geriatric Cognitive Disorders Extra, 2*, 219-228. http://dx.doi.org/10.1159000338378

CHAPTER II

Domain-Specific Cognitive Changes in Persons with COPD: A Systematic Review and Meta-Analysis

COPD is a major cause of disability and is the third leading cause of death in 2014 (CDC, 2016). It is estimated that 15 million people or 6.4% of the U.S. population have been diagnosed with COPD and more than 50% of persons with low pulmonary function were not aware that they have COPD indicating that the number of persons with COPD may be even higher (CDC, 2016). Not only does COPD limit airflow and cause breathing difficulties, it has been associated with extrapulmonary effects including cognitive decline. There is compelling evidence that persons with COPD have a higher prevalence of cognitive decline when compared to general population. Cognitive decline has been reported in 22% - 77% of patients with COPD (Ambrosino, Bruletti, Scala, Porta, & Vitacca, 2002; Grant, Heaton, McSweeny, Adams & Timms, 1982; Heaton, Grant, McSweeney, Adams, & Petty, 1983; Incalzi et al., 2002) while 10 – 20.3% of general population has been reported to have cognitive decline (Langa & Levine, 2014; Luck et al., 2016). There is also strong evidence that persons with COPD have a greater risk of developing cognitive decline compared to the age matched controls decline (Hung, Wisnivesky, Siu, & Ross, 2009; Singh et al., 2014; Thakur, 2010). There are inconsistencies in the evidence related to the prevalence and risk of cognitive decline in persons with COPD. The wide variation in the estimated prevalence and risk of cognitive decline may be attributed to selection of neuropsychological measures and inclusion criteria such disease severity. When global measures of cognition were used, the results were little (5.5%) to no significant difference in cognitive decline between persons with COPD and control groups

(Incalzi et al., 2002; Isoaho, Puolijoki, Huhti, Laippala, & Kivela, 1996; Stuss, Peterkin, Guzman, Guzman, & Troyer, 1977, Thakur et al., 2010). In contrast, using a neuropsychological battery showed a longer prevalence of cognitive decline in persons with COPD. In hypoxemic COPD, 48.5% - 77% of persons had cognitive decline in all abilities it was not equal across all domains of cognition (Cleutjens et al., 2017; Grant et al., 1982; Incalzi et al., 1993). These results indicate that the selection of neuropsychological measures and disease severity may explain a portion of the variation in the estimated prevalence and risk of cognitive decline. Most of these studies support a negative association between COPD and performance in cognitive domains but the domains measured often vary between studies. The variation in the selection of the domains included in studies may be explained by a variety of classification systems. There is a lack of a universal classification for cognitive domains in research (Dodd, Getov & Jones, 2010). To develop a better understanding of the effect of COPD on cognitive domains, in a systematic review, Torres- Sanchez et al. (2015) classified the cognitive domains as proposed by Lezak (2004 as cited in Torres-Sanchez et al. 2015) which included the domains: perception, attention, memory and learning, executive function and language. There were 34 different neuropsychological tests used to evaluate the six cognitive domains (p. 188). Yet, cognitive decline was prevalent in all domains on at least one test. The use of both a variety of cognitive domain classification systems and the neuropsychological tests leads to a variation in prevalence and risk of cognitive decline across studies. Because of the importance of cognition in daily life and the proliferation of research examining the relationship between COPD and domain-specific cognition, we sought to advance the science by conducting a systematic review to determine what is known about the extent of domain-specific cognitive decline in persons with stable COPD. In addition to the domain classification used by Torres-Sanchez et al. (2105), we added the domain of processing speed. Processing speed is a process that underlies

many of the other cognitive processes and is frequently found in literature. To our knowledge, this is the first meta-analysis of this literature. The aim of the systematic review was to synthesize the state of current knowledge regarding the extent of domain-specific cognitive decline in relationship to the various stages of COPD. The aim of this meta-analysis review was to address two questions: 1) what are the effect sizes of any decline in the cognitive domains of perception, attention, memory and learning, executive function and language in persons with COPD? 2) Is age or disease severity a moderating factor?

Methods

Data sources and search strategy

We utilized standard systematic review methodology following the handbook from the Cochrane Collaboration (Higgins & Green, 2008). The manuscript follows the PRISMA statement for reporting systematic reviews and meta-analysis (Liberti et al., 2009). The guidance of a professional librarian was sought. A systematic approach was used to complete the search using the following search strings (comprising terms related to COPD, cognition and domain-specific cognition): chronic obstructive airway disease (COAD) “COAD, COPD, emphysema or chronic bronchitis”; AND “cognition”, “cognitive function”, “executive function”, ”perception”, “attention”, “memory”, “working memory”, “visual memory”, “verbal memory”, “reaction time”, “processing speed”, “language”, “visuospatial”, “cognitive dysfunction”, “cognitive deficit”, and “cognitive domains” (for more information see Appendix F: Search Terms). The search was limited to humans and English language. The following databases were systematically searched: PubMed, CINAHL, Scopus, Psych Info, Web of Science, and Sociological Abstracts. Ancestry searches were performed on authors from all eligible studies

seeking any previous work. Hand search was completed on all bibliographies from selected studies. The bibliographic details of all retrieved studies were stored in a Ref Word-COS file. Duplicate records that were retrieved from various data bases were removed

Study selection

Three reviewers (JS, GN & JA) conducted of independent title and abstract screening of 2295 studies retrieved from the database searches using specific inclusion criteria guidelines (for more information see Appendix G: Table 12 G. 1: Study Selection Tool). Two independent reviewers evaluated the retrieved studies and determined inclusion or exclusion based on predefined selection criteria. In the advent of non-agreement, JL a fourth reviewer made the determination for inclusion. We included studies in the systematic review if they fulfilled the following criteria:

1. Studies of persons with COPD included one of cognitive domains of interest.
2. Studies in which the research design was descriptive, experimental, quasi-experimental.
3. Participants: major focus of the article was persons with COPD/chronic bronchitis/emphysema defined by any of the following measures: FEV_1 or FEV_1/FVC, arterial blood gases, diffusion capacity, lung volumes or self-report of diagnosis.
4. A healthy control group or age referents normal were reported for the neuropsychological test measured.
5. Domain-specific cognition: the article had to include at least one of the following domains: perception; attention; memory and learning; executive function, language or processing speed.
6. No date restriction was imposed.

7. Studies were limited to English language and humans.

Studies that reported the Mini-Mental Status Exam (MMSE) as the sole assessment tool for cognition and used the components of the MMSE as cognitive domains were excluded from systematic review and meta-analysis. The MMSE is a useful screening tool for differentiating individuals with serious neurocognitive impairments from healthy controls, but it has ceiling effects, poor test-retest reliability, is insensitive to subtle brain morphology and individual items demonstrate limited construct validity (Spencer et al., 2013). Additionally, the MMSE is insensitive to impairment in attention and executive function which are two of the main deficits associated with COPD (Villeneuve et al., 2012). Eighty-seven studies deemed potentially eligible by at least one reviewer were retrieved. From the 87 studies, 27 studies were selected to be included in the systematic review. Studies were selected from the systematic review to be included in the meta-analysis if the data for at least one cognition domain was reported with mean and standard deviation. A total of 14 studies were included in the meta-analysis. In each domain, three studies using the same measure of cognition were required to perform the meta-analysis. The flow diagram for the search is depicted in Figure 2 (see Figure 2 Flow Diagram of Systematic Search).

Data extraction and quality assessment.

The results of the data extraction were summarized in structured tables, one for each cognitive domain. A meta-analysis was performed for each cognitive domain that reported findings from at least three studies using comparable measurements. The data was analyzed using Comprehensive Meta-Analysis Software Version 3. The fixed effect model was used to estimate the effect size in the various cognitive domains. The data are presented with standardized mean differences (SMD); less than 0.39 was considered small effect, 0.4 - 0.7 a

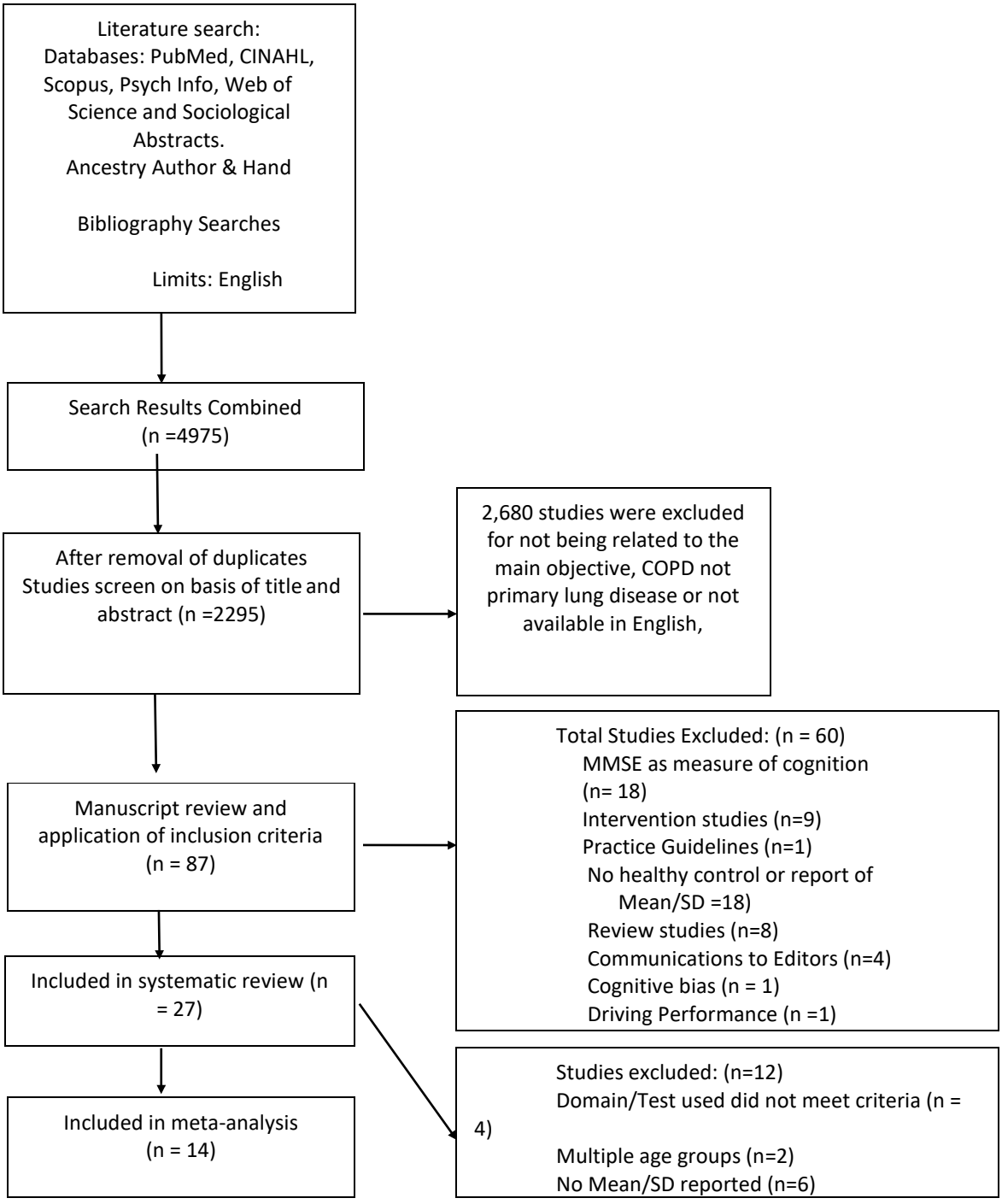


Figure 2 Flow Diagram of Systematic Search

moderate effect and more that 0.7 a large effect (Higgins & Green, 2008). To assess for publication bias funnel plot or Egger's regression test was used as appropriate. However, due to the small number of articles that were included in each analysis, a funnel plot or Egger's regression test could not be performed. To test for heterogeneity the I^2 was performed for quantifying the ratio of heterogeneity to total variation in observed effects. The thresholds that were used for the interpretation of I^2 were: 0-40% might not be important. To be consistent in describing the information obtained from each included study, a tool was developed based on Effective Practice and Organization of Care from the Cochrane Collection (EPOC, 2013) (for more information see Appendix H: Table 13 H. 1: Data Extraction Tool). Quality of the research was assessed using the appropriate Scottish Intelligence Guideline Network (SIGN) methodology checklist (Sign Checklist, 2004) (for more information see Appendix I SIGN checklist). Using the checklist, studies were ranked as high quality (++), acceptable (+) or unacceptable (0). No articles reviewed were deemed of an unacceptable quality. All studies included in this review were of acceptable to high quality.

Results

Perception

Results yielded 2 studies that examined perception (for more information see Appendix J: Table J. 14 Perception Studies). Three different instruments were used in assessing perception. The results from these studies were mixed. There was insufficient data from the studies to perform analysis for effect size.

Attention

The search yielded 16 studies that examined attention (for more information see Appendix K: Table 15 K. 1 Attention Studies). Eight different measurements were used in assessing attention. The results were mixed. Although finding from two of the

tests, Stroop Test and Digit Vigilance Test, were each used in two studies with no significant difference found between groups. The Seashore Rhythm Test was used in three studies with mixed results. However, a meta-analysis could not be performed as one study (Grant, et al. 1982) did not report mean and standard deviation. Of these eight measurements, only the TMT A met the criteria to be included in the meta-analysis. Ten studies used the TMT A. The results were mixed. Of these, five studies were excluded from the meta-analysis: one (Bratek, et al., 2013) reported the mean time to complete the assessment but did not report the standard deviation or the significance; two studies (Favalli, et al., 2008; Liesker, et al. 2004) reported the results as median and range and two studies (Dal Ben & Bricolo, 2012; Dal Negro et al., 2014) reported results in decades of age resulting in multiple age brackets and no summary report for the groups. In addition, Dal Ben & Bricolo (2012) when assessing cognition with TMT-A, reported cognitive performance was significantly impaired in persons with COPD in all ages of life yet the means scores for age groups 40 - 49 and 50 - 59 indicated that persons with COPD performed better than healthy controls as evidenced by lower reported mean time in seconds to complete the task.

A meta-analysis was performed which included five studies that measured attention using the TMT A. The sample size was 209 COPD and 146 controls. The results showed that persons with COPD had higher score or poorer performance than the controls. There was a moderate summary effect size was found, -0.516, 95% CI [-0.747 – - 0.286], z = -4.395, p = 0.00. Test for heterogeneity $I^2 = 40.467$, (see Figure 3: Forest Plot: Attention - TMT-A).

Memory and Learning

The search results yielded 19 studies that examined memory and learning (for more information see Appendix L: Table 16 L. 1: Memory and Learning Studies). Thirteen

different measurements were used in assessing memory and learning. The results of the studies were mixed for either immediate or delayed recall.

Wechsler Memory Scale III- logical memory test was used in two studies with results indicating persons with COPD having significantly poorer memory. Three studies used Raven's Colored Progressive Matrices. The results were mixed. A meta-analysis could not

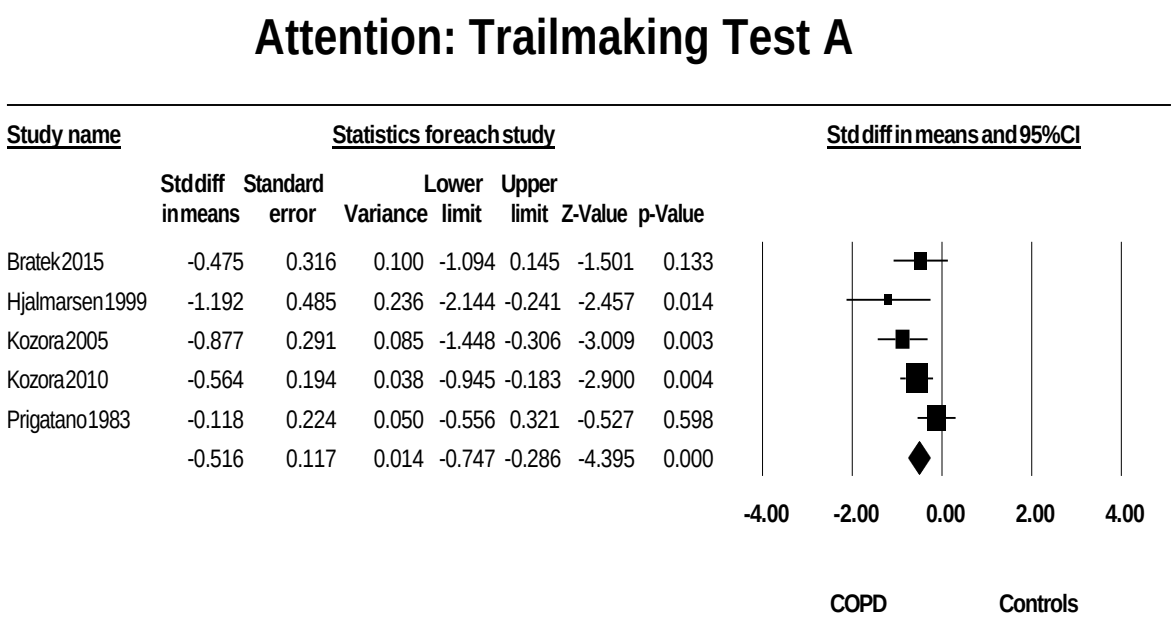


Figure 3 Forest Plot: Attention-TMT-A

be performed on attention measured by Raven's Colored Progressive Matrices as one study (Favalli et al, 2008) reported results in median and range. Five studies used the Wechsler

Memory Scale Revised. The test has seven subsets each requiring the participant to recall and to retell certain details. In reporting the results of the test, the descriptive labels were not consistent across studies making alignment for meta-analysis difficult. Three of the five studies reported a significant difference. Three studies used Rey Auditory Verbal Learning, but the descriptive labels were not consistent across studies making alignment for meta-analysis difficult. All three studies reported a significant difference between groups. Two measurements met the criteria to be included in the meta-analysis: Digit Span Forward and Wechsler Memory Scale. Nine studies used span forward to assess short term memory span. Two of these studies were excluded from the meta-analysis: one used verbal span forward (Incalzi et al., 1993) and the other did not report results in mean and standard deviation (Cleutjens et al., 2014). Six studies used the Wechsler Memory Scale for assessing immediate and delayed recall. Two of these studies were excluded from the meta-analysis: immediate and delayed recall. Two of these studies were excluded from the meta-analysis: one was excluded as the results were reported in percentage loss (Grant et al., 1982) and one reported visual memory not verbal memory (Zhang et al., 2013).

In the digit span forward test for memory and learning, sample size COPD 254 and controls 232, persons with COPD had lower scores than controls; small summary effect size - 0.297, 95% CI [-0.480 - - 0.114], z = - 3.187, p = 0.001 and I^2 = 33.755, (see Figure 4: Forest Plot: Memory and Learning - Digit Span Forward). Persons with COPD had lower scores compared to controls on measures of immediate and delayed recall than controls. The sample was COPD 364 and controls 249. The moderate summary effect size for immediate recall was - 0.603, 95% CI [-0.794 – -0.412], z = -6.174, p = 0.00, I^2 = 57.5, (see Figure 5: Forest Plot: Memory and Learning - Immediate Recall). In delayed recall, there was a moderate

summary effect size for delayed recall: - 0.420, 95% CI [-0.610 - -0.231, z = -4.344, p = 0.00, I^2 = 61.05 (see Figure 6: Forest Plot: Memory and Learning - Delayed Recall).

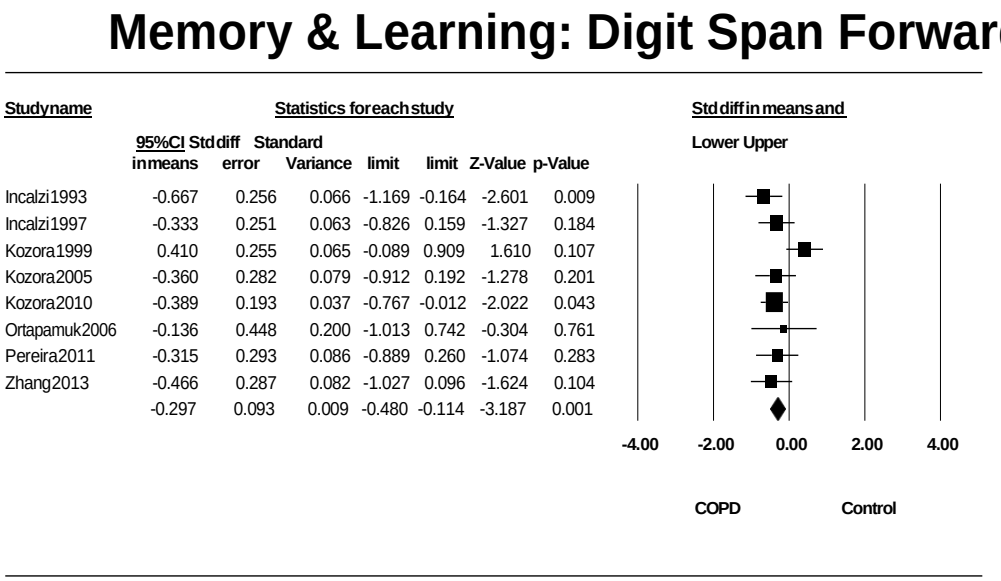


Figure 4: Forest Plot: Memory & Learning - Digit Span Forward

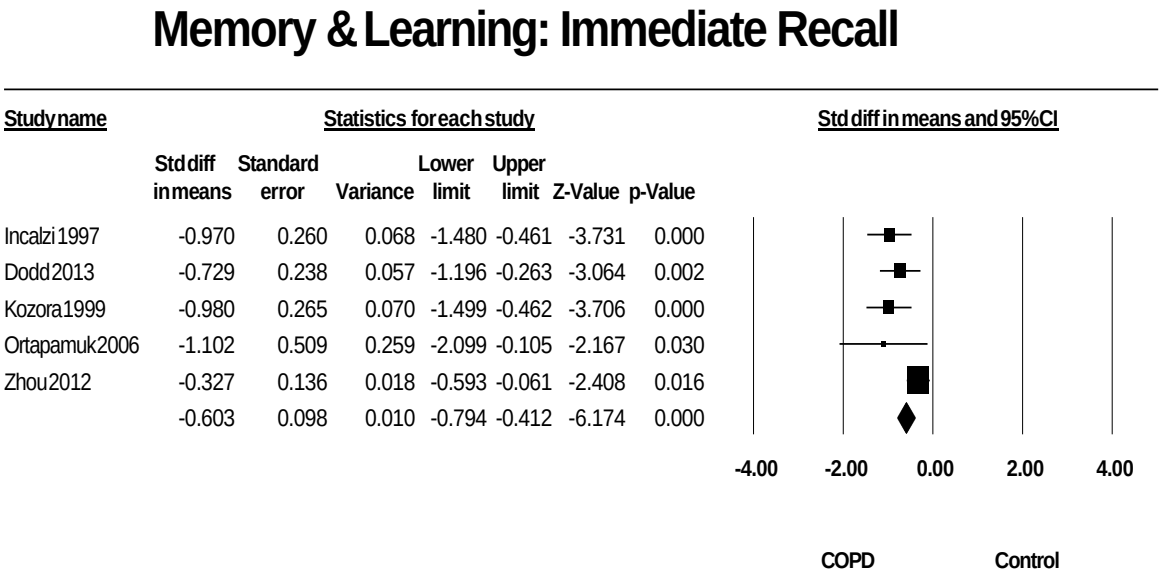


Figure 5: Forest Plot: Memory and Learning Word List Immediate Recall

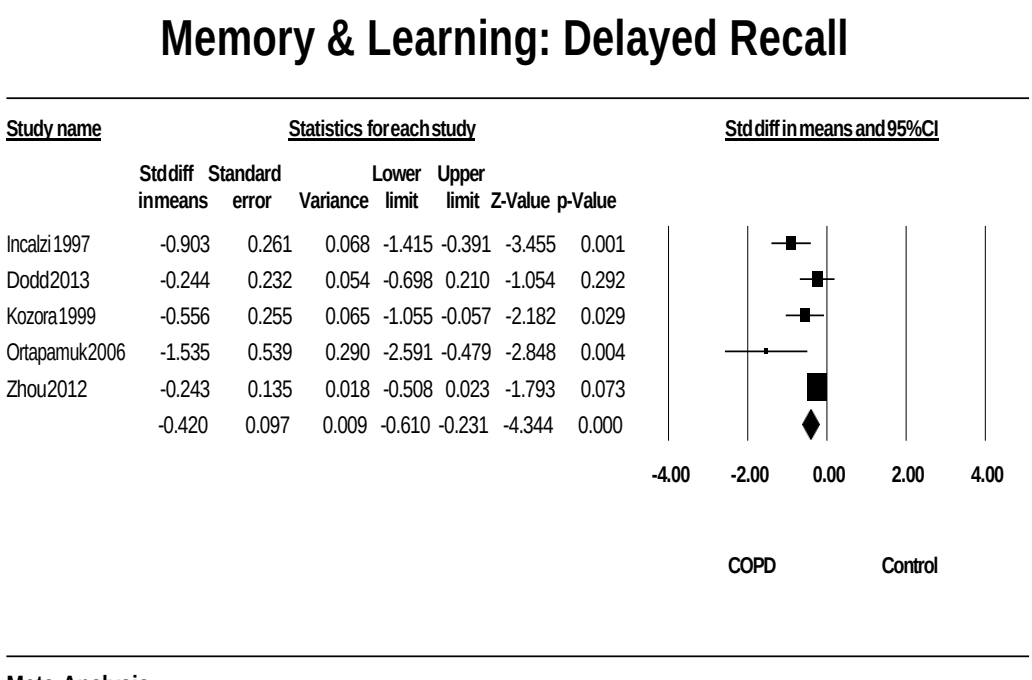


Figure 6 Forest Plot: Memory and Learning - Delayed Recall Word List

Executive Function

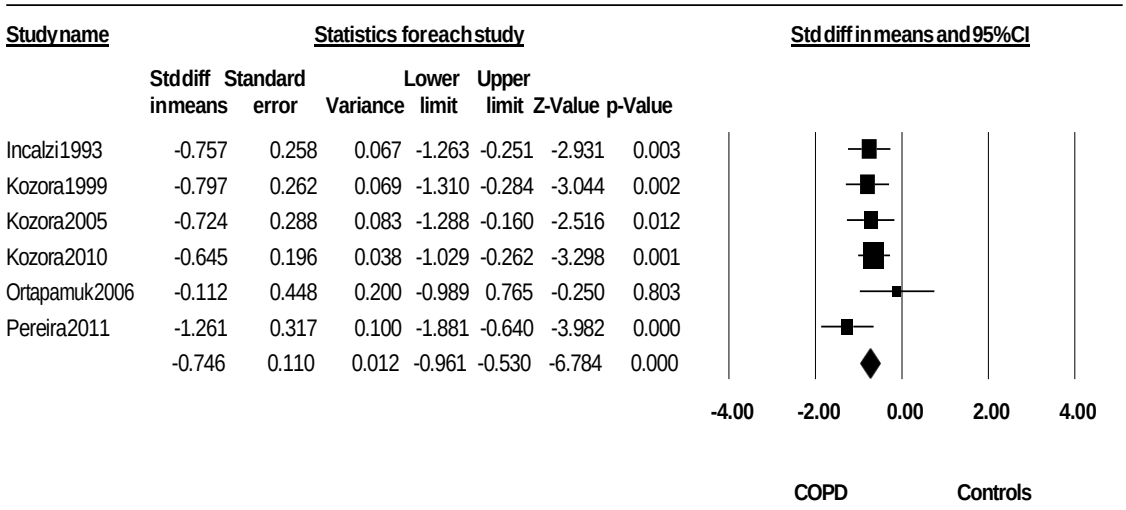
The search yielded 22 studies which examined executive function (for more information see Appendix M: Table 17 M. 1: Executive Function Studies). Eight different instruments were used to measure executive function. Regardless of the instrument used, the results were mixed. One study reported fluid intelligence with no significant difference noted between the groups (Cleutjens et al., 2014). Corse-Block Reverse Spatial Span (Incalzi et al., 1993) and Standard Progressive Matrices (Klein et al., 2010) were each used in one study with persons with COPD having lower scores than controls. Copying Design was used in two studies with mixed results (Incalzi et al. 1993, Ortapamuk & Naldoken, 2006). WAIS Similarities was used in three studies but could not be included in the meta-analysis due to methods of reporting. One study indicated there was no difference between groups and the other two studies did not report the significance level (Hjalmarsen et al, 1999; Kozora et al.,

2005: Kozora et al., 2010). The results of studies of executive function are mixed even within the same cognitive test was used.

Four measures of executive function were included in enough studies to be included in the meta-analysis: verbal fluency letter, verbal fluency animal, digit span backward and TMT B. Nine studies measured verbal fluency letters and/or animals to assess executive function. One study was excluded from meta-analysis as it used a test of verbal fluency called Delis-Kaplan which differed from the other studies (Dodd, et al., 2013). Eight studies assessed executive function with verbal fluency letters. Two studies were excluded: one study reported medians and ranges (Favalli et al, 2008) and in another study (Kozora et al., 2002) the verbal fluency letter was part of a controlled oral word association test. Five studies assessed executive function with verbal fluency animals. One study (Favalli et al, 2008) was excluded as it reported medians and ranges.

The sample size for letter fluency was COPD 185 and controls 142 and for animal fluency COPD 253 and controls 239. Person with COPD had lower scores on both letter fluency and animal fluency than controls. There was a large summary effect size for letter fluency was - 0.746. 95% CI [-0.961 - -0.530], z = -6.784, p = 0.00. Test for heterogeneity I^2 = 0, (see Figure 7 Forest Plot: Executive Function - Letter Fluency). There was no significant difference between persons with COPD and controls on verbal fluency animal test - 0.136, 95% CI [-0.368 - -0.097], z = -1.144, p = 2.53. Test for heterogeneity I^2 = 51.938, (see Figure 8 Forest Plot: Executive Function – Verbal Fluency Animal).

Executive Function Verbal Fluency Letter



Meta-Analysis

Figure 7 Forest Plot: Executive Function - Verbal Fluency Letter

Executive Function Verbal Fluency Animal

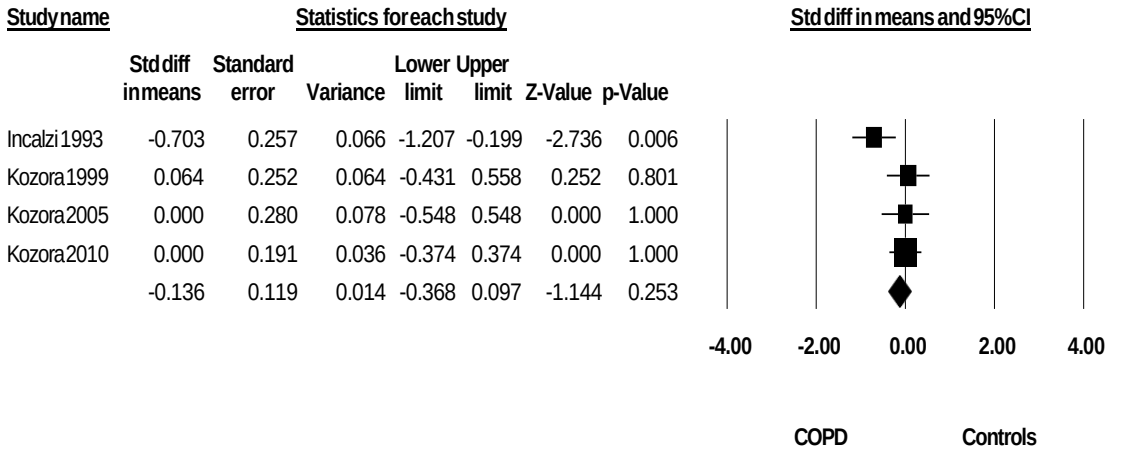


Figure 8 Forest Plot: Executive Function- Verbal Fluency Animal

Five studies used digit span backwards. The sample size was COPD 143 and controls 122. There was a small summary effect – 0.352, 95% CI [-0.106 - - 2.80], p = 0.005, I^2 = 60. Persons with COPD performed lower than controls (see Figure 9: Forest Plot: Executive Function - Digit Span Backward).

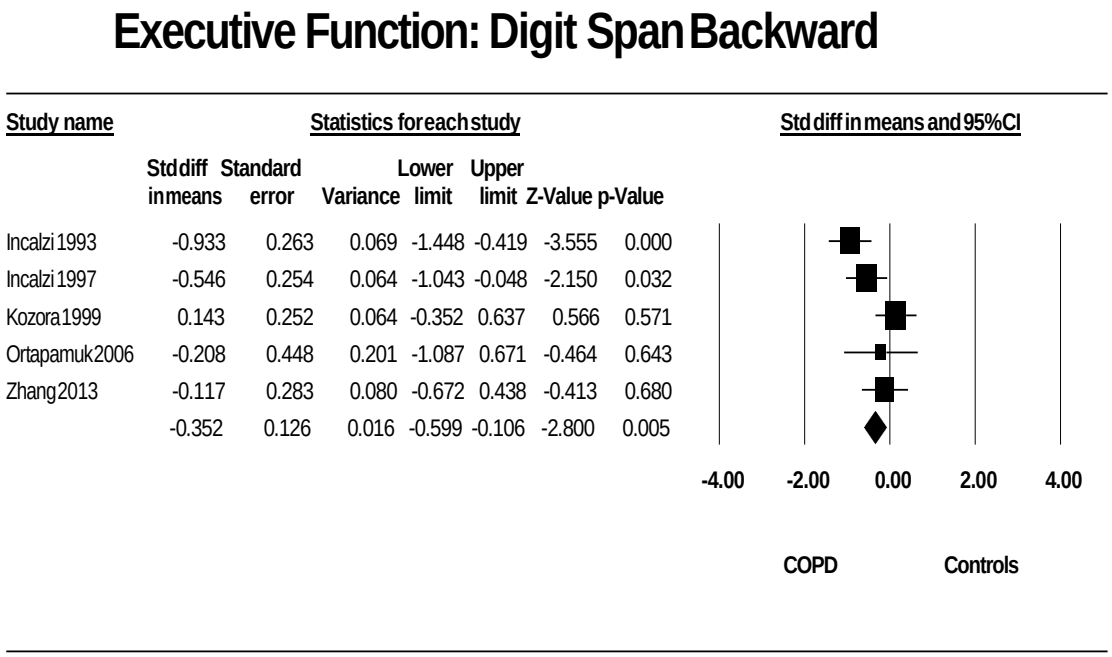


Figure 9 Forest Plot: Executive Function - Digit Span Backward

Fourteen studies used TMT B. Seven were excluded: five because mean and standard deviation were not reported (Bratek, et al., 2013; Favalli, et al., 2008; Grant et al, 1982; Liesker, et al., 2004; Shim et al., 2001); two reported by age group categories (Dal Ben & Bricolo, 2012; Dal Negro, et al., 2014). From the seven studies included in the meta-analysis, the sample size was 180 COPD and 198 controls. Persons with COPD had lower scores than controls on the TMT B, (see Figure 10: Forest Plot: Executive Function – TMT-B). There was a moderate effect -0.572, 95% CI [-0.769 – -0.374], z = - 5.674, p = 0, I^2 = 36.45.

Executive Function: Trailmaking B

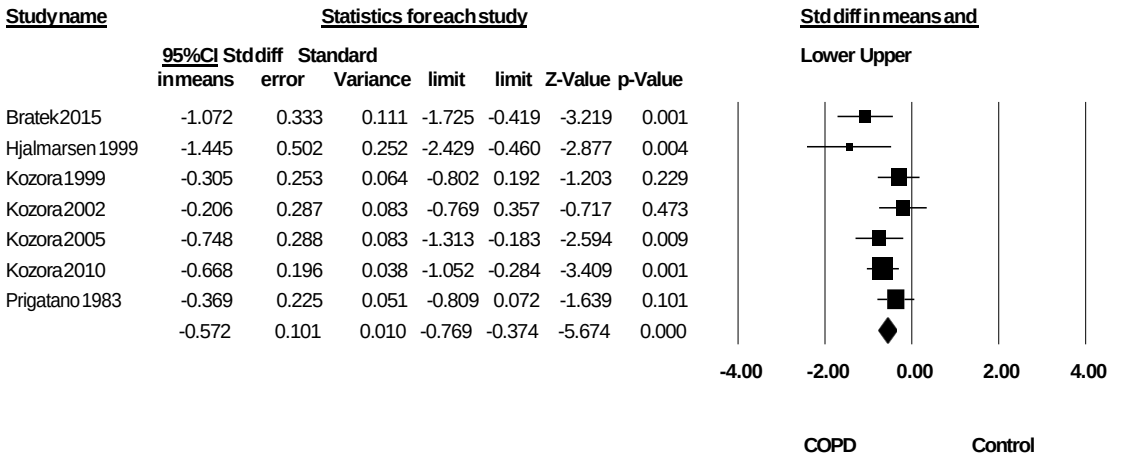


Figure 10 Forest Plot: Executive Function - TMT-B

Language

Five studies compared language abilities between persons with COPD and healthy controls (for more information see Appendix N: Table 18 N. 1: Language Studies). Two different measurements were used. Two studies used the Aphasia Screening Test with mixed results (Grant et al., 1982; Prigatano et al., 1983). Three studies used the Boston Naming and were included in the meta-analysis. There was no significant difference from person with COPD and controls. Summary estimate was -0.239, CI 95% [- 0.502 – 0.025], z = - 1/777, p = 0.076, $I^2 = 0$ (see Figure 11: Forest Plot Language - Boston Naming).

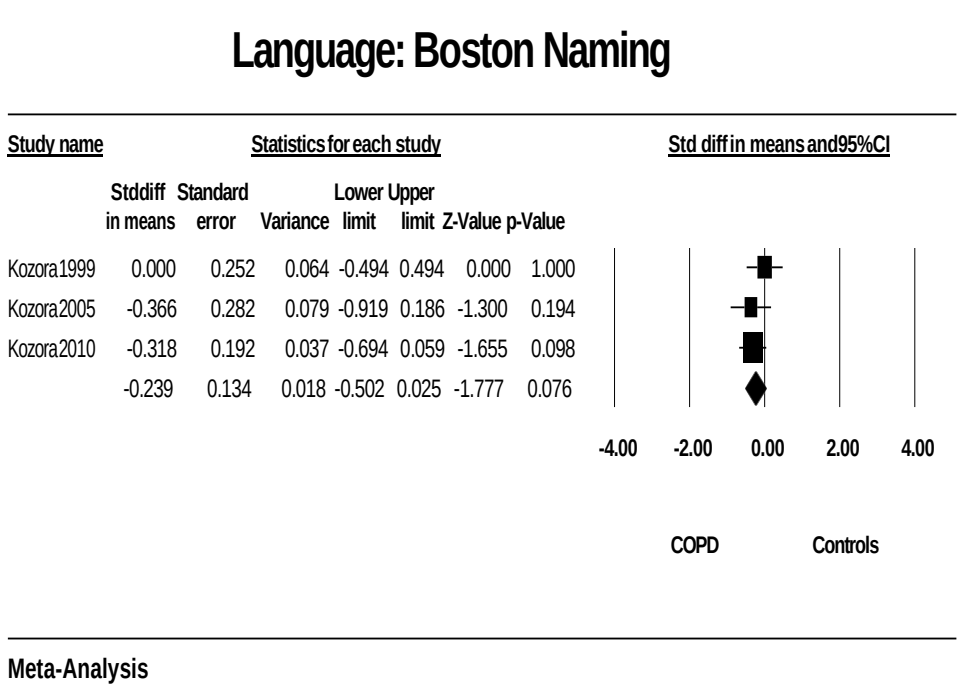


Figure 11: Forest Plot: Language - Boston Naming

Processing Speed

The search yielded nine studies that examined processing speed in persons with COPD compared to controls (for more information see Appendix O: Table 19 O. 1: Processing Speed Studies). Five different measurements were used in assessing processing speed. Of these measurements, six studies used digit symbol. The sample size was 214 COPD and 167 controls Persons with COPD had lower scores on digit symbol than controls. There was a large effect size -0.923, 95% CI [-1.148 - -0.698], z = - 8.043, p = 0.00 with $I^2 = 0$ (see Figure 12: Forest Plot: Processing Speed - Digit Symbol).

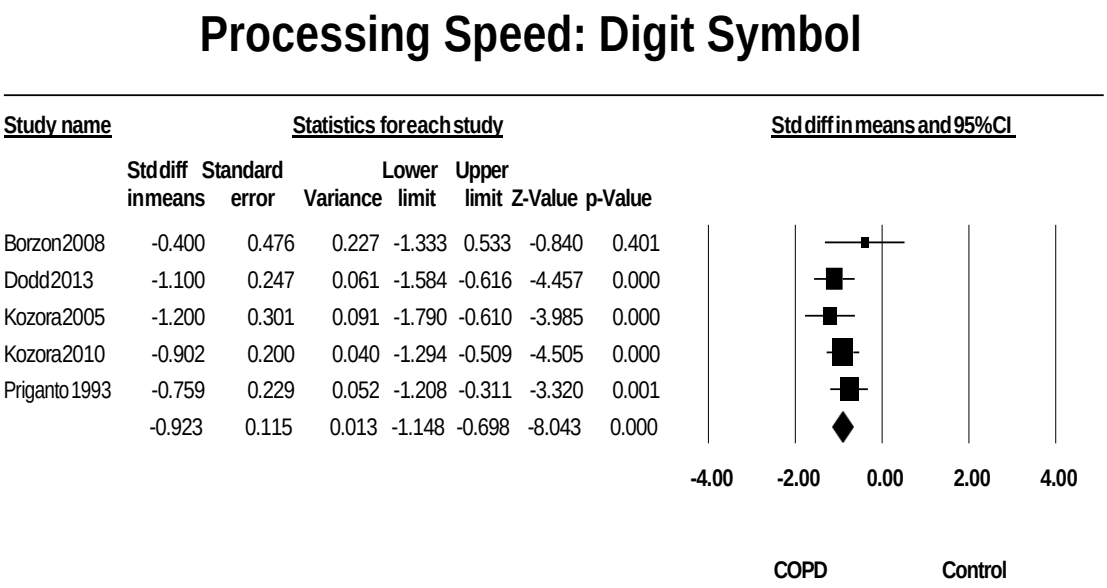


Figure 12: Forest Plot: Processing Speed - Digit Symbol

Discussion

We found that changes in cognition do not occur equally across all cognitive domains. Additionally, the findings were inconsistent. The more frequently a cognitive domain was studied, the greater the number of measurements used, the greater the inconsistencies in the findings. We found that in all domains if the effect size was significant, it was also negative indicating persons with COPD had poorer performance in the cognitive domain of interest. In summary 1) attention (TMT-A) had a moderate effect 2) memory and learning had a moderate effect in immediate and delayed recall (Wechsler Memory Scale) and a small effect in short-term memory span (Digit Span Forward) 3) executive function had a large effect (verbal fluency letter), moderate effect (TMT B), small effect (digit span backwards) and not significant (verbal fluency animal) 4) language effect was not significant (Boston naming) and 5) processing speed had a large effect (digit symbol). These findings show there is a decline in cognitive domains of

attention, memory and learning, executive function and processing speed but based on effect size, the decline is not equal. There is also variation within domains when assessed with more than one measurement. The greatest inconsistency in effect size was in executive function. In the test of verbal fluency, a relatively large difference between frequency of letter and category animal are not uncommon with 10% of sample have a letter fluency to animal score difference of 18 or more words (Strauss, Sherman & Spreen, 2006). To perform the semantic fluency tasks, it requires four retrieval components 1) activation automatically spreading from the cue, 2) self-monitoring of output to prevent repetition and error, 3) suppression of previously retrieved response and 4) generation of cues to access new names. Words that start with a letter compared to words that are in a certain category are potentially stored different. Thus, in animal fluency, a person may have to switch categories more frequently decreasing the number of words named (Strauss et al, 2006). One explanation for the inconsistency is that within each cognition domain several processes occur. The term executive function is an umbrella term that includes a wide range of cognitive and behavioral processes such as reasoning, problem-solving, planning, ability to sustain attention, utilization of feedback, multitasking, cognitive flexibility and the ability to deal with novelty (Chan, Shum, Toulopoulou & Chen, 2008), There is also an emotional component to executive function which relates to the experience of reward and punishment, regulations of one's social behavior and decision making involving emotional and personal interpretation (Chan, 2008). It is possible that some processes within the domain demonstrate a larger decline than others. Deficits in executive function can interfere with a person's daily life. Understanding the relationship between the decline of a component of executive function and its impact on daily life is important for patient education. Additionally, the domain of executive function may need to be examined within a context-specific situation of living with COPD. For

example, a person with COPD has fluctuating symptoms and must frequently problem-solve to determine when to take additional prescribed medication such as a rescue inhaler or decide when it is time to seek medical treatment. Given the wide range of processes included in executive function, to understand the impact of decline that occurs in COPD, it may be beneficial to exam only a certain component of executive function such as problem solving. The decrease in cognitive function can impact the severity of COPD by interfering with optimal self-management. According to Emery, Finkel & Penderson (2012) the relationship between COPD and decreased cognitive function is a directional relationship, a decrease in pulmonary function leads to subsequent decrease in cognitive function but there is no evidence that a decline in cognition can lead to a decline in pulmonary function. It is posited that a decline in cognitive function decreases a person's ability to perform the necessary patient-initiated treatments for managing their COPD. This in turn can lead to further decline in pulmonary function.

Cognitive decline in COPD can increase the risk of having a further decline in pulmonary function. When using dry powder inhalers, in subjects with an MMSE score between 10 -24, the higher the score on the MMSE or the better the cognitive function, the better the performance in self-administering dry powdered inhalers (Fraser, Patel, Norkus & Whittington, 2012) but those with a MMSE score less than were rarely able to develop the ability to learn to use a metered dose inhaler (Allen, Warwick-Sanders & Baxter, 2009). In another study of proper inhaler use found in persons with COPD that were competent in the acquisition and short-term retention of inhaler on a test for frontal executive function the EXIT25, had a score of < 15(Allen, Jain, Ragab, & Malik, 2003). These studies support the finding that declines in cognitive domains interfere with the ability to acquire the skills needed to monitor and administer airway medications. COPD and the comorbidity of cognitive decline may lead to an increase in health

care utilization and mortality, but evidence is mixed. Individuals with both COPD and cognitive decline had a 48% higher rate of all cause hospitalizations and a rate of death nearly three times as high as the risks for COPD or cognitive decline alone (Chang, Chen, McAvay, & Tinetti, 2012). In contrast, other studies have found no association between executive function, frequency of hospitalization and survival in persons with COPD (Dodd et al., 2015; Fix, Daughton, Kass, Bell & Golden, 1985). Further researcher is needed to examine the relationship among COPD, cognitive decline and utilization of healthcare. As these relationships are better understood, interventions could be tailored to decrease hospital re-admissions in the COPD population. There were several limitations in this study. While the search was extensive, within each domain there were a small number of studies to be analyzed. One factor that limited the studies included in the analysis of each domain was the variety of neuropsychological tests used. We also had too few studies to exam the mediator effects of disease severity and age. Additionally, power could not be assessed do to the small number of studies and the lack of a clear-cut point for a specific score on the neuropsychological tests that would indicate a functional decline would be noted. There was evidence of decline in all cognitive domains except language. The largest effect size was found in the domains of executive function and processing speed. Further research needs to be done to connect the significant findings in cognitive decline with changes in the functional performance. As a better understanding occurs between domain-specific cognitive decline and their relationship to functional performance, strategies can be developed to optimize cognitive performance and compensate for losses.

BIBLIOGRAPHY

Allen, S. C., Jain, M., Ragab, S., & Malik, n. (2003). Acquisition and short-term retention of inhaler techniques require intact executive functioning elderly subjects. *Age and Ageing, 32,* 299-302.

Allen, S. C., Warwick-Sanders, M., & Baxter, M. (2009). A comparison of four tests of cognition as predictors of inability to learn to use a metered dose inhaler in old age. *The International Journal of Clinical Practice, 63*(8), 1150-1153.

Ambrosino, N., Bruletti, G., Scala, V., Porta, R., & Vitacca, M. (2002). Cognitive and perceived health status in patient with chronic obstructive pulmonary disease surviving acute on chronic respiratory failure: a controlled study. *Intensive Care Medicine, 28,* 170-177. http://dx.doi.org/10.1007s00134-1165-6

Borson, S., Scanlan, J., Friedman, S., Zuhr, E., Fields, J., Aylward, E., . . . Yeh, S. (2008). Modeling the impact of COPD on the brain. *Int J Chron Obstruct Pulmon Dis, 3*(3), 429-434.

Bratek, A., Zawada, K., Beil-Gawelczyk, J., Beil, S., Sozanska, E., Krzysztof, K., . . . Pierzchala, W. (2015). Depressiveness, symptoms of anxiety and cognitive dysfunctions in patients with asthma and chronic obstructive pulmonary disease (COPD): possible associations with inflammation markers: a pilot study. *J Neural Transm, 22*(122 (suppl)), S83-S91. http://dx.doi.org./10.10007/s00702-014-1171-9

Bratek, A., Zawada, K., Barczyk. A., Szanska, E., Sozanska, E., Krzysztof, K., . (2013). Analysis of Psychoemotional State and Intellectual Abilities in Patients with Asthma and Chronic Obstructive Pulmonary Disease - Primary Results. *Psychiatric Danubina, 25*(Suppl 2), 207- 211.

CDC. (2016). Center for Disease Control and Prevention: Chronic Obstructive Pulmonary Disease (COPD) Retrieved from https://www.cdc.gov/copd/index.html

Chan, R., Shum, D., Toulopoulou, T., & Chen, E. (2008). Assessment of executive functions: Review of instruments and identification of critical issues. *Archives of Clinical Neuropsychology. 23.* 201-216. http://dx.doi.org/doi:10.1016/j.acn.2007.08.010

Chang, S., Chen, S., McAvay, G., & Tinetti, M. (2012). Effect of Coexisting Chronic Obstructive Pulmonary Disease and Cognitive Impairment on Health Outcomes in Older Adults. *JAGS, 60,* 1839-1846. http://dx.doi.org/10.111/j.1532-5415.2012.04171.x

Cleutjens, F. A., Spruit, M. A., Ponds, R. W., Dijkstra, J. B., Franssen, F. M., Wouters, E. F., & Janssen,D. J. (2014). Cognitive functioning in obstructive lung disease: results from the United Kingdom biobank. *J Am Med Dir Assoc, 15*(3), 214-219. http://dx.doi.org/10.1016/j.jamda.2013.12.007

Cleutjens, F. A., Franssen, F. M., Spruit, M. A., Vanfleteren, L., Gijsen, C., Dijkstra, J. B., . . . Janssen, D.J. (2017). Domain-specific cognitive impairment in patients with COPD and control subjects. *International Journal of Chronic Obstructive Pulmonary Disease, 12,* 1-11. http://dx.doi.org./10.2147/COPD.S119633

Cooper, H. (2010). *Research Synthesis and Meta-Analysis: A Step-by-Step Approach. (Applied Social Research Methods).* 4th ed. Los Angeles, CA: Sage.

Crisan, A. F., Oancea, C., Timar, B., Fira-Mladinescu, O., Crisan, A., & Tudorache, V. (2014). Cognitive impairment in chronic obstructive pulmonary disease. *PLoS ONE, 9*(7), e102468. http://dx.doi.org/10.1371/journal.pone.0102468

Dal Ben, S., & Bricolo, F. (2012). The Psychological and Cognitive Profile. In Dal Negro, R., & Hodder, R. (Eds.). *Long-Term Oxygen Therapy: New Insights and Perspectives.* 67-74. Milan, Italy: Springer.

Dal Negro, R. W., Bonadiman, L., Tognella, S., Bricolo, F. P., & Turco, P. (2014). Extent and prevalence of cognitive dysfunction in chronic obstructive pulmonary disease, chronic non-obstructive bronchitis, and in asymptomatic smokers, compared to normal reference values. *Int J Chron Obstruct Pulmon Dis, 9,* 675-683. http://dx.doi.org/10.2147/COPD.S63485

Dal Negro, R., Bonadiman, L., Bricolo, F., Tognella, S., & Turco, P. (2015). Cognitive Dysfunction in severe chronic obstructive pulmonary disease (COPD) with or without Long-Term Oxygen Therapy (LTOT). *Multidisciplinary Respiratory Medicine.* 10 - 17. http://dx.doi.org/10.1186/s40248-015-0013-4

Dodd, J. W., Getov, S. V., & Jones, P. W. (2010). Cognitive function in COPD. *Eur Respir J, 35*, 913- 922. http://dx.doi.org/10.1183/09031936.00125109

Dodd, J. W., Charlton, R., van den Broek, M., & Jones, P. W. (2013). Cognitive Dysfunction in Patients Hospitalized with Acute Exacerbation of COPD. *CHEST, 144*(1), 119-127.

Dodd, J. W., Novotny, P., Sciurba, F., Benzo, R., & Group, N. R. (2015). Executive Function, Survival and Hospitalization in Chronic Obstructive Pulmonary Disease. *Ann AM Thorac Soc, 12*(10). http://dx.doi.org/10.1513/AnnalsATS.201506-373)C

Effective Practice and Organization of Care (EPOC). Data collection form. EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services; 2013. Retrieved: *http://epoc.cochrane.org/epoc-specific-resources-review-authors*

Emery, C. F., Finkel, D., & Pedersen, N. (2012). Pulmonary Function as a Cause of Cognitive Aging.*Psychological Science, 23*(9), 1024-1032. http://dx.doi.org/10.1177/0956797612439422

Favalli, A., Miozzo, A., Cossi, S., & Marengoni, A. (2008). Differences in neuropsychological profile between healthy and COPD older persons. *Int J Geriatr Psychiatry, 23*(2), 220-221. http://dx.doi.org/10.1002/gps.1847

Fioravanti, M., Nacca, D., Amati, S., Buckley, A., & Bisetti, A. (1995). Chronic Obstructive Pulmonary Disease and Associated Patterns of Memory Decline. *Dementia, 6*, 39-48.

Fix, A., Daughton, D., Kass, I., Bell, C., & Golden, C. (1985). Cognitive Functioning and Survival Among Patients with Chronic Obstructive Pulmonary Disease. *Intern. J. Neuroscience. 27.* 13-17.

Fraser, M., Patel, M., Norkuw, E., & Whittington, C. (2012). The Role of Cognitive Impairment in the Use of the Diskus Inhaler. *JAMDA. 13.* 390-393. http://10.1016/j.jamda.2011.04.004

Grant, I., Heaton, R., McSweeny, J., Adams, K., & Timms, R. (1982). Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease. *Arh Intern Med, 142*, 1470-1476.

Hjalmarsen, A., Waterloo, K., Dahl, A., Jorde, R., & Viitanen, M. (1999). Effect of Long-Term Oxygen Therapy on Cognitive and Neurological Dysfunction in Chronic Obstructive Pulmonary Disease. *European Neurology. 47.* 27-35.

Heaton, R., Grant, I., McSweeny, J., Adams, K., & Petty, T. (1983). Psychologic Effects of Continuous and Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Pulmonary Disease. *Acrh Intern Med, 143*, 1941-1947.

Higgins, J., & Green, S. (Eds.). (2008). *Cochrane Handbook for Systematic Reviews of Interventions*.Hoboken, New Jersey: Wiley and Sons.

Hung, W., Wisnivesky, J., Siu A., & Ross, J. (2009). Cognitive Decline among Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory Critical Care Medicine, 180*, 134-137. http://dx.doi.org/10.1164/rccm.200902-0276OC

Incalzi, R.A., Germma, A., Marra, C., Muzzolon, R., Capparella, O. & Carbonin, P. (1993). Chronic obstructive pulmonary disease. An original model of cognitive decline. *Am Rev Respir Dis. 148*(2). 418-424.

Incalzi, R. A., Gemma, A., Marra, C., Capparella, O., Fuso, L., & Carbonin, P. (1997). Verbal Memory Impairment in COPD: Its Mechanisms and Clinical Relevance. *CHEST, 112*, 1506-1513.

Incalzi, R. A., Bellia, V., Maggi. S., Imperiale, C., Capparella, O., Catalano, R., Carbonin, P., Rengo, F., & the Sa.R.A. (Salute Respiratoria nell'Anziano) Study Group. (2002). Mild to moderate chronic airways disease does not carry an excess risk of cognitive dysfunction. *Aging Clin Exp Res, 14*(5), 395-401.

Isoaho, R., Puolijoki, H., Huhti, E., Laippala, P., & Kivela, S. (1996). Chronic Obstructive Pulmonary Disease and Cognitive Impairment in the Elderly. *International Pyschogeriatrics, 8*(113-125).

Klein, M., Gauggel, S., Sachs, G., & Pohl, W. (2010). Impact of chronic obstructive pulmonary disease (COPD) on attention functions. *Respiratory Medicine, 104*, 52-60. http://dx.doi.org/10.1016/j.med.2009.08.008

Kotterba, S., Rasche, K., Widdig, W., Blombach, S., Duchna, K., Duchna, H., . . . Malin, J. (1998). Vigilance and Neuropsychological Capacity in Obstructive Sleep Apnea Syndrome and Chronic Obstructive Pulmonary Disease. *Somnologie, 2*, 117-122.

Kozora, E., Filley, C., Julian, L., & Cullum, M. (1999). Cognitive Functioning in Patients with Chronic Obstructive Pulmonary Disease and Mild Hypoxemia Compared with Patients with Mild Alzheimer Disease and Normal Controls. *Neuropsychiatry, Neuropsychology and Behavioral Neurology. 12* (3). 178-181.

Kozora, E., Tran, Z., & Make, B. (2002). Neurobehavioral Improvement After Brief Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease. *journal of Cardiopulmonary Rehabilitation. 22.* 426.430.

Kozora, E., Emery, C., Ellison, M., Wamboldt, F., Diaz, P., & Make, B. (2005). Improved Neurobehavioral Functioning in Emphysema Patients Following Lung Volume Reduction Surgery Compared with Medical Therapy. *CHEST. 128.* 2653-2663.

Kozora, E., Emery, C. F., Kaplan, R. M., Wamboldt, F. S., Zhang, L., & Make, B. J. (2008). Cognitive and Psychological Issues in Emphysema. *Proc Am Thorac Soc, 5*, 556-560. http://dx.doi.org./10.1513/pats.200708

Kozora, E., Emery, C., Zhang, L., & Make, B. (2010). Improved Neurobehavioral Functioning in Emphysema Patients Following Medical Therapy. *Journal of Cardiopulmonary Rehabilitation and Prevention. 30.* 251-259.

Langa, K., & Levine, D. (2014). The Diagnosis and Management of Mild Cognitive Impairment: A Clinical Review. *JAMA. 312*(23). 2551-2561. http://dx.doi.org/jama.2014.13806

Liberati, A., Altman, D., Tetzlaff, J., Mulrow., C., Gotzsche, P., Ioannidis, J., Clarke, M., Devereaux, P., Kleijnen, J., & Moher, D. (2009). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PloS Medicine. 6* (7). e1000100. http://dx.doi.org/10.1371/journal.pmed.1000100

Liesker, J., Postma, D., Beukema, R., ten Hacken, N., van der Molen, T., Riemersma, R., van, Zomeren, E., & Kerstjens, H. (2004). Cognitive performance in patients with COPD. *Respiratory Medicine, 98*, 351-356. http://dx.doi.org/10.1016/j.med.2003.1.004

Luck, T., Then, F., Schroeter, M., Witte, V., Engel, C., Loeffler, M., Thiery, J., Villringer, A. & Riedel- Heller, S. (2016). Prevalence of DSM-% Mild Neurocognitive Disorder in Dementia-Free Older Adults; Results of the Population-Based LIFE-Adult-Study. *Am J Geriatr Psychiartry.25*(4). 328-339. http://dx.doi.org/10.1016/j.jagp.2016.07.001.

Okubadejo, A. A., O'Shea, L., Jones, P. W., & Wedzicha, J. A. (1997). Home assessment of activities of daily living in patients with severe chronic obstructive pulmonary disease on long-term oxygen therapy. *Eur Respir J, 10*, 1572-1575.

Ortapamuk, H., & Naldoken, S. (2006). Brain perfusion abnormalities in chronic obstructive pulmonary disease: comparison with cognitive impairment. *Annals of Nuclear Medicine, 20*(2), 99-106.

Pereira, E., Vianna, C., Taunay, T., Sales, P., Lima, J., & Holanda, M. (2011). Improvement of Cognitive Function After a Three-Month Pulmonary Rehabilitation Program for COPD Patients. *Lung. 189.* 279-285.

Prigatano, G., Parsons, O., Levin, D., Wright, E., & Hawryluk, G. (1983). Neuropsychological Test Performance in Mildly Hypoxemic Patients with Chronic Obstructive Pulmonary Disease. *Journal of Consulting and Clinical Psychology. 51*(1). 108-116.

Rafnssom, S., Deary, I., Smith, G., Whiteman, M., Rumley, A., Lowe, G., & Fowkes, G. (2007). Cognitive Decline and Markers of Inflammation and Homeostasis: The Edinburgh Artery Study. *Journal of American Geriatrics society. 55*(5). 700-707. http://dx.doi.org/10.111/j.153- 5415.2007.01158.x

Shim, T., Lee, J., Kim, S., Lim, T., Kim, S., Kim, S., & Kim, W. (2001). Cerebral Metabolic Abnormalities in COPD Patients Detected by Localized Proton Magnetic Resonance. Spectroscopy. *CHEST. 120.* 1506-1513.

SIGN Checklist. Scottish Intelligence Guideline Network. Retrieved http://www.sign.ac.uk/pdf/sign50annexc.pdf

Singh, B., Parsaik, A., Mielke, M., Roberts, R., Scanlon, P., Geda, Y., . . . Peterson, R. (2013). Chronic Obstructive Pulmonary Disease and Association with Mild Cognitive Impairment: The Mayo Clinic Study of Aging. *Mayo Clin Poc, 88*(11), 1222-1230. http://dx.doi.org/10.1016/j.mayocp.2013.08.012

Singh, B., Mielke, M., Parsaik, A., Cha, R., Roberts, R., Scanion, P., . . . Peterson, R. (2014). A Prospective Study of Chronic Obstructive Pulmonary Disease and the Risk for Mild Cognitive Impairment. *JAMA Neurol, 71*(5), 581-588. http://dx.doi.org./10.001/jamaneurol.2014.94

Spencer, R., Wendell, C., Giggey, P., Katzel, L., Lefkowitz, D., Siegel, E., & Waldstein, S. (2013). Psychometric Limitations of the Mini-Mental State Examination Among Nondemented Older Adults: An Evaluation of Neurocognitive and Magnetic Resonance Imaging Correlates. *Experimental Aging Research. 39*(4). 382-397. http://dx.doi.org/10.1080/0361073X.2013.808109

Strauss, E., Sherman, E., & Spreen, (2006). *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary.* 3rd ed. New York, New York: Oxford.

Stuss, D., Peterkin, I., Guzman, D., Guzman, C., & Troyer, A. (1997). Chronic obstructive pulmonary disease: Effects of hypoxia on neurological and neurophychological measures. *Journal of Clinical and Experimental Neuropsychology. 19*(4). 515-524. http://dx.doi.org/10.1080/01688639708403741

Thakur, N., Blanc,P., Julian L., Yelin, E., Katz, P, Sidney, S., Iribarren, C., & Eisner, M. (2010). COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. *International Journal of Chronic Obstructive Pulmonary Disease, 5*, 263-269.

Torres-Sanchez, I., Rodriquiez-Alzueta, E., Cabrera-Martos, I., Lopez-Torres, I., Moreno-Ramirez, M., & Valenze, M. (2015). Cognitive Impairment in COPD: a systematic review. *J Bras Pneumol, 41*(2), 182-190. http://dx.doi.org/10.1590/S1806-37132015000004424

Villeneuve, S., Pepin, V., Rahayel, S., Bertrand, J., de Lorimier, M., Rizk, A., Desjardins, C., Parenteau, S., Beaucage, F., Joncas, S., Monchi, O., & Gagnon, J. (2012). Mild Cognitive Impairment in Moderate to Severe COPD: A Preliminary Study. *CHEST. 142* (6). 1516-1523.

Vos, P., Folgering, H., & van Herwaarden, C. (1995). Visual attention in patients with chronic obstructive pulmonary disease. *Biological Psychology, 41*, 295-305.

Zhang, H., Lin, W., Sun, Y., Yang, T., Zheng, S., Fan, M., and Zhang, J. (2013). Reduced Regional Gray Matter Volume in Patients with Chronic Obstructive Pulmonary Disease: A Voxel-based Morphometry Study. *AJNR Am J Neuroradiol 34.* 334-339. http://dx.doi.org/10.3174/ajnr. A3235

Zhou, G., Liu, J., Sun, F., Xin., X., Duan, L., Zhu, X., & Shi, Z. (2012). Association of Chronic Obstructive Pulmonary Disease with Cognitive Decline in Very Elderly Men. *Dementia and Geriatric Cognitive Disorders Extra, 2*, 219-228. http://dx.doi.org/10.1159000338378

CHAPTER III

The Relationship between Length of Time with COPD and Changes in Domain-Specific Cognition, Functional Performance, and Life Satisfaction: The Health and Retirement Study

Cognitive function is important to successful aging. Cognitive function consists of the complex processes by which an individual perceives, registers, stores, retrieves and uses information from the environment to adapt behavior to new situations (Dodd, Getov, & Jones, 2010). To provide more information about the nature of cognitive function, cognitive processes have been separated into discrete domains. COPD has a negative impact on domain-specific cognition. Although there are inconsistencies in findings, there is strong evidence that person with COPD have lower scores in most domains cognition. Compared to those without COPD, persons with COPD were found to have significantly poorer performance in the domains of attention (Grant, Heaton, McSweeny, Adams, Timms., 1982) short-term memory (Cleutjens et al., 2014; Favalli et al., 2008; Fioravanti, Nacca, Amati, Buckley & Bisetti, 1995; Incalzi et al., 1997), long-term memory (Cleutjens et al., 2014; Favalli et al., 2008; Incalzi et al., 1997), executive function (Dal Negro et al., 2014, Favalli, et al., 2008), language (Favalli, et al., 2008) and processing speed (Cleutjens et al, 2014). These results suggest that all domains of cognition may be affected by COPD. As COPD progresses in severity, so does the decline in cognition. Several studies found that persons with higher disease severity had greater cognitive decline (Crisan et al., 2014; Dal Negro, Bonadiman Tongnella, Bricolo, & Truco, 2014; Fioravanti et al., 1995; Incalzi et al., 2002; Singh et al., 2014). Other studies found no relationship between

markers of disease severity and cognitive decline (Grant et al., 1982; Thakur et al., 2010). Several studies found the prevalence of cognitive decline dramatically increases with worsening hypoxemia and hypercapnia (Grant et al., 1982; Krop, Block, & Choen, 1973; Prigatano, Parson, Lein, Wright & Hawryluk, 1983). In persons with hypoxemic COPD, 48.5% - 77% had cognitive decline in all abilities but the magnitude was not equal across all domains of cognition (Cleutjens et al., 2017; Grant et al., 1982; Incalzi et al., 1993). Independent of hypoxemia and disease severity, in persons with acute exacerbation of COPD, 57% were in the impaired range and 20% were considered to have suffered pathological loss in processing speed (Dodd, Charlton, van den Broek, & Jones, 2013). These results suggest that there is a strong relationship between disease severity and declines in domain-specific cognition. The preponderance of these studies was cross sectional, providing little information regarding the change in cognition that occurs over time with advancing disease. A few studies have examined differences in global cognition over time. In a 15-month study incident MCI and MCI subtypes, persons with COPD had a higher rate of developing MCI than did controls (Singh, 2014). A study from the HRS data base found when comparing baseline and two to six years later in persons with and without COPD, persons with COPD had a significantly greater decline than persons without COPD (1 point to 0.7 points respectively) (Hung, Wisneivesky, Siu, & Ross, 2009). In a 3-year longitudinal study, there was no difference in global cognition but persons with COPD had greater declines in immediate and delayed memory, language (word fluency) and attention (digit symbol) (Zhou et al., 2012), Thus, longitudinal data regarding cognitive decline is very limited but the evidence suggests that there is a different trajectory in the development of cognitive decline in the presence of COPD. There is a strong body of evidence describing a decrease in functional performance and a small body of evidence that supports the notion that a decline in cognition contributes to functional decline.

The annual rate of decline in functional performance is approximately 3% (Kapella, Larson, Covey & Alex, 2011). Two studies examined the capacity or capability to perform activities at baseline and two years later. At baseline 26% of persons with COPD had disability or a decrease in capacity or capability to perform activities and 10.5% developed functional disability over the course of the study (Eisner et al., 2011). In other study, there was a difference of prevalent disability (dependency in at least one ADL) between persons with COPD and those without (12.8% and 5.2% respectively) and over two years 9.2% of those with COPD developed a disability above baseline compared to 4% in those without COPD (Martinez, Richardson, Han & Cigolle, 2014). In addition, persons with coexisting COPD and MCI had a greater risk developing disability (OR, 2.7) compared to COPD alone (OR, 1.9) or MCI alone (OR 2.0) (Martinez et al., 2014). These studies support that not only does functional performance decline with COPD; the decline is greater in the presence of cognitive decline. To depict the relationships between domain-specific cognition, functional performance, and life satisfaction for this portion of the study a modified visual representation of Cognition, Functional Performance, and Life Satisfaction was created (see Figure 13 Visual Representation of Cognition, Functional Performance, and Life Satisfaction Modified for Longitudinal Study). Two frameworks guided this work; Revised Wilson & Cleary Model of Health-Related Quality of Life (Ferrans et al., 2005) (see Appendix A for more information on Revised Wilson & Cleary Model of Health-Related Quality of Life) and Functional Status Framework (Leidy, 1994). The revised Wilson & Cleary Model of Health-Related Quality of Life illustrates the dynamic interactions between health, functioning, and life satisfaction (Ferrans et al., 2005). The Functional Status Framework defines functional performance as "those activities that people do in the normal course of their lives to meet basic needs and fulfill usual roles and maintain health

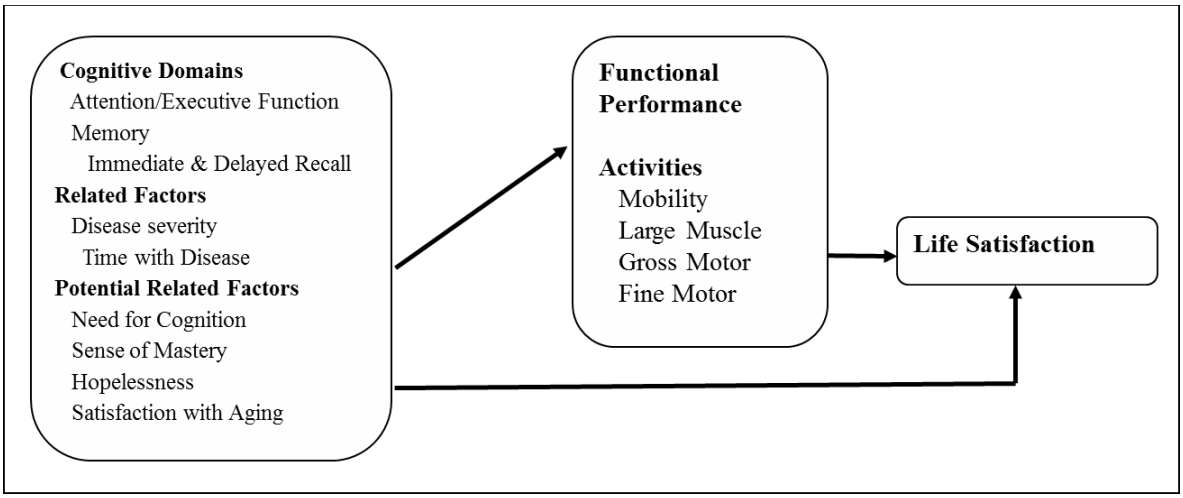


Figure 13 Visual Representation of Cognition, Functional Performance and Life Satisfaction Modified for Longitudinal Study

and well-being" (Leidy, 1994, p. 197.). Life satisfaction is subjective well-being related to how happy or satisfied someone is with various aspects of their lives (Ferrans et al., 2005).

Psychosocial factors could influence cognition. For purpose of this work we will focus on perception of the need for cognition, sense of mastery, hopelessness, and satisfaction with aging. The need for cognition is "the tendency for an individual to engage in and enjoy thinking" (Cacioppo, Petty & Kao, 1984). It impacts behaviors that in turn affect behaviors that have an impact on cognitive performance.

The sense of mastery is the belief that one has the skills and abilities to achieve a goal. One of the best predictors of success in goal attainment is an individual belief that they have control in their lives (Daniel, Brown, Dhurrkey, Cargo, & O'Dea, 2006). Higher levels of mastery are associated with better health, more health-promoting behaviors, increased memory and cognitive function (Colcombe & Kramer, 2003; Lachman & Andreoletti, 2006). Lower levels of mastery have been associated with perceived stress and subjective memory complaints (Daniel et al., 2006; Lee & Kim, 2014). The sense of mastery is a potentially modifiable variable that has been associated with memory, cognitive function, and health.

Hopelessness is a negative perspective concerning the future. A sense of hopelessness has been identified as a predictor of future poor health and social functioning (Pompili et al., 2013). The presence of feelings of hopelessness, when measured in midlife, is a predictor of cognitive impairment an average of 21 years later (Håkansson, Soininen, Winblad, & Kivipelto, 2015). Thus, exploration of the relationship between hopelessness and domain-specific cognition could add to the understanding of cognitive decline in persons with COPD.

Satisfaction with aging is one's self-perception of aging or an individual's beliefs about their aging (Levy, Slade & Kasl, 2002). Satisfaction with aging is a social psychological predictor of disabilities. Attitudes towards aging develop over one's lifetime. A person's attitude toward aging is derived from encounters with older people and current societal attitudes towards aging. When these attitudes are internalized, they become part of one's self and the expectations for the trajectory of one's aging process. When one reaches late adulthood, the positive or negative expectations are likely to be experienced impacting both cognitive and physical functioning (Levy et al., 2002). Thus, determining the strength of the relationship between satisfaction with aging and domain-specific cognitive function in persons with COPD is of interest.

The decline in domain-specific cognition and functional performance in presence of COPD has been well established. However, there is very limited information regarding change in domain-specific cognition over time and the impact that this change has on functional performance and life satisfaction. To our knowledge, there is only one study that has longitudinally examined domain-specific cognition in COPD and had a duration of three years with the mean age of the participants of 80 years old (Zhou et al., 2012). Our aim is to

expand the knowledge related to longitudinal effects on domain-specific cognition in persons with COPD. The primary aim of this research was to describe the relationship cognition over time for people with COPD and a non-COPD group. The secondary aims were determining if functional performance mediates the relationship between domain-specific cognition and life satisfaction and exploring the relationship between the psychosocial variables and cognitive function. The working hypotheses are: (1) there is a positive relationship between the length of time with COPD and decline in domain-specific cognition in persons with COPD (2) functional performance mediates the relationship between cognitive function and life satisfaction and (3) the psychosocial variables; need for cognition, sense of mastery, hopelessness and satisfaction with aging impact domain-specific cognition.

Methods

Data Source

We used data from the HRS, a population-based nationally representative, biennial longitudinal health survey initiated in 1992. The HRS is a public use data set that is produced and distributed by the University of Michigan with funding from the Nations Institute on Aging (grant number NIA U01AG009740). The HRS is managed jointly through a cooperative agreement between the National Institute on Aging (NIA) and the Institute for Social Research (ISR) at the University of Michigan (HRS). The HRS was approved by the Health Science Institutional Review Board at the University of Michigan. Two data sets were used from the HRS; the HRS 2014 Final Release wave 12 and the RAND HRS Data, Version P. The RAND HRS data is produced by the RAND Center for the Study of Aging, Santa Monica CA with funding from the NIA and the Social Security Administration, (August 2016).

For this study, cross-sectional data was drawn from the HRS 2014 data set. The 2014 data set was also used to identify person with COPD. After identification of having COPD, a backward process was used to identify the first interview in which the participant self-reported the diagnosis of COPD. This interview was labeled zero for baseline and each subsequent interview was consecutively by twos to correlate with the biennial data collection times. For the non-COPD group, the first interview was labeled zero for baseline complete longitudinal data analysis, the two databases were merged to provided data from 1992-2014. Due to differences in cognitive measures data, years 1992 and 1994 were excluded from analysis. Participants are residents of the United States over the age of 50.

Inclusion criteria/ Exclusion criteria

Two groups were established: COPD and non-COPD. For both groups, data were included in this study if the participants were alive at the time of the 2014 interview, completed the survey without a proxy, and between the ages of 65-89 which corresponds with the HRS data collection for cognitive function. To be included in the COPD group, the participant must self-report that a doctor told them that they had a chronic lung disease such as chronic bronchitis or emphysema, not including asthma. The first year of self-reported COPD had to be identifiable. To be included in the non-COPD group, the participant must currently be a non-smoker. Data from both groups were excluded if the participant was residing in a nursing home, self-reported a history of stroke, Alzheimer's disease, dementia, or taking medication prescribed by their primary care provider for Alzheimer's disease, dementia or memory problem.

Persons with COPD were identified in 2014 and followed backwards into the study to determine first self-report of COPD. This was labeled baseline and then each subsequent

year was labeled consecutively. For the non-COPD group identified in 2014, their first interview was labeled baseline and each subsequent year labeled consequently. The final sample size at baseline was 3070 non-COPD and 380 with COPD. The groups were followed for seven-time periods or 12 years.

Measurements of Domain-specific Cognition.

The HRS includes a variety of measures to assess domain-specific cognition. The domains tested are attention/executive function, immediate and delayed memory, knowledge, language and orientation, abstract reasoning, fluid reasoning, and vocabulary. (for more information see Appendix P: Table 20 P .1 Selected HRS Measures). Cognitive measures have changed over the course of the study. The cognitive domains and their measures that have remained consistent across time are executive function measured by serial sevens subtractions, and memory and learning as measured by immediate and delayed recall.

Attention/Executive function. The HRS uses serial seven subtractions were used to assess attention/executive function. In serial seven subtractions, the participant is asked to subtract seven from 100 and continue subtracting seven from each following answer for a total of five times. American Psychiatric Association Diagnostic and Statistical Manual, 5th edition (DSM-5) defines inattention as the reduced ability to direct, focus, sustain and shift attention. Serial seven subtractions has a sensitivity of 97.7%, 95% CI [78.1 - 99.9], specificity 13.7% 95% CI [8.9 – 19.8], positive predictive value 13.2%, 95% CI [8.4 – 19.3%] and negative predictive value 95.8, 95% CI [78.9 - 99.9%] (Voyer et al., 2006). It should be noted that serial sevens are strongly associated with arithmetic ability and results should be used with caution (Karzmark, 2000). In the HRS data set, serial seven subtractions have the highest quantity of missing data with appropriately 10% refusing to subtract sevens and those who refused had lower

performance on the other cognitive test (Herzog & Wallace, 1997). Thus, the rate of decline may be greater than depicted in this study.

Memory and Learning. In the HRS, memory and learning are assessed by word list recall, immediate and delayed. To avoid practice effect, the HRS contains four different word lists (Lachman & Andreoletti, 2006). For immediate word recall, the participant was read a list of ten nouns and asked to recall as many as possible in any order immediately. Delayed recall is, after approximately five minutes, the participant was asked to remember the same nouns given in immediate recall. Both immediate and delayed recall are scored as the count of the number of correct responses, 0-10. Word list recall has a test-retest reliability of 0.70 -0.79 (Strauss et al., 2006).

Measurements of Related Factors

Disease Severity. The HRS does not identify the severity of COPD. The length of time a person had COPD was used as a proxy for disease severity. Time one for COPD was created by identifying the first self-report of COPD. Time one for the non-COPD group was the first year in the study. In both groups, after defining time one, all subsequent interviews were sequentially numbered.

Depression. Depression was measured with the Center for Epidemiology Studies Depression Scale (CES-D). The CES-D is 20-item scale measuring symptoms of depression in nine different groups as defined by the DSM-V including sadness or dysphoria, loss of interest or anhedonia, appetite, sleep, thinking/concentration, guilt or worthlessness, tired or fatigue, movement or agitation and suicidal ideations. The scores are summed across all 20 items with higher scores indicating greater depressive symptoms. The CES-D has high internal consistency across studies with Cronbach's alpha coefficient ranging from 0.85 – 0.90 (Radloff, 1977). The

CES-D is sensitive for detection of depressive symptoms and change in symptoms over time (Weissman, Sholomskas, Pottenger, Prusoff & Locke, 1977).

Anxiety. On the HRS survey, anxiety is a single-item of self-report responding to a history of ever having had an anxiety disorder

Sleep. The HRS has four items which were used to quantify difficulties with sleep. The items included trouble falling asleep, difficulty staying asleep, waking up too early and not being able to go back to sleep and restless sleep. Responses are on a four-point Likert scale: most of the time, sometimes, rarely or never. The items were re-coded into dichotomous variables of any difficulty or no difficulty. A composite score, sleep disturbance score was created from these variables.

Measurements of Potential Related Factors

The Psychosocial and Lifestyle Questionnaire, a leave behind self-assessment survey, is administered to half of the persons in the HRS study biennially. It includes the variables perception of the need for cognition, sense of mastery, hopelessness, satisfaction with aging and the life satisfaction Scale. Only the cross-sectional data from the year 2014 was included in the analysis. Of the persons eligible to complete the leave behind the survey, the response rate for 2014 was 77.8% (Smith, Ryan, Sonega & Weir, 2017).

Need for Cognition. The HRS need for cognition scale is composed of six items. Six items selected for the "Need for Cognition" scale were based on research from the CogUSA project (Smith et al., 2017). Need for cognition contains two dimensions: cognitive enjoyment and cognitive effort (for more information see Appendix P: Table 20 P. 1 Selected HRS Measures). Content validity for 2014 survey cognitive enjoyment Cronbach's α =0.83 and the cognitive effort Cronbach's α = 0.80 (Smith et al., 2017).

Sense of Mastery. The HRS sense of mastery scale is composed of five items. The five items on the scale are answered using a 6-point Likert Scale. An index is created by averaging the 5 items (for more information see Appendix P: Table 20 P.1 Selected HRS Measures). The reliability for the sense of mastery scale was reported as Cronbach's α 2014 survey = 0.91 (Smith et al., 2017).

Hopelessness. The HRS hopelessness scale consists of two items from Everson et al. (1997) and two items form Beck et al. (1974) (as cited in Smith, 2017) (for more information see Appendix P: Table 20 P. 1 Selected HRS Measures). A hopelessness index is created by averaging the scores across all items. The reliability is reported with Cronbach's α 2014 survey = 0.88 (Smith et al., 2017).

Satisfaction with aging. HRS Satisfaction with aging assesses eight areas that provide positive and negative experiences of aging (HRS) (for more information see Appendix P: Table 20 P. 1 Selected HRS Measures). The reliability of aging satisfaction is reported for is 2014 survey is Cronbach's α = .82, for positive aging satisfaction Cronbach's α = .77 and negative aging satisfaction, Cronbach's α = .77 (Smith et al., 2017).

Measurements of Functional Performance

Activities. The following four items from the HRS were used to measure functional performance activities: mobility, large muscles, gross motor skills, fine motor skills (for more information see Appendix P: Table 20 P. 1 Selected HRS Measures). These activities were chosen to be included in the HRS as they were found to be the activities needed to perform ADLs and IADLs (HRS). Mobility includes five activities measuring ability walk and climb stairs for various distances. Large muscle skills include sitting for two hours, ability to get out of chair, kneel and stoop and push or pull large objects. Gross motor skill has overlap with mobility on ability to walk but only refers the distance of one block and adds transferring out of

bed and bathing. Fine motor skills include picking up a dime, dressing and eating. The items were re-coded into dichotomous items: any difficult with activity with the score of "1" and no difficulty with an activity score of "0". A total functional performance score was created by adding the scores across the activities. The reliability of the physical functioning measures was Cronbach's 0.92 (Fonda & Herzog, 2004).

Measurement of Life Satisfaction

On the HRS, life satisfaction is reported as a score on a Likert scale. The respondent is asked to rate how satisfied they are with life ranked on a five-point Likert scale anchored with completely satisfied and not at all satisfied (for more information see Appendix P: Table 20 P. 1 Selected HRS Measures).

Analyses

Statistical analysis was performed using STATA 15.0 (STATA Corp, 2017). The statistical analysis used includes baseline comparisons between groups using chi-square for count variables and independent sample t tests for continuous variable. Prior to performing t-tests, Levene's test for unequal variance were performed. All reported p-values are two-sided, and results are considered statistically significant at $p < 0.05$.

Separate mixed-effects Poisson models were used to describe the relationship between the number of years since self-reported diagnosis of COPD and the change in cognitive function over time compared to non-COPD group. The Poisson models compared the longitudinal changes in domain-specific cognition (one per outcome e.g. executive function) by group (COPD, non-COPD). We centered the time variable on the subjects' first self-report of COPD for COPD subjects and the first interview for non-COPD group. Each model was fully factorialized, and included a fixed main effect parameter comparing COPD versus non-COPD, fixed effects parameters comparing person's first reported outcome to

each subsequent observation, and importantly, the simple interaction effects comparing the change in domain-specific cognition outcome among COPD participants relative to non-COPD We included a-priori contrasts evaluating the omnibus effects of time (i.e. change overall) and the omnibus interaction effects (group differences over all time points), and we interpret the simple effects parameters only then the omnibus effects are significant. Each model included a random Y-intercept term to accommodate the longitudinal (i.e. repeated measures) experimental design. Our initial evaluations of these models revealed significant variability difference in outcomes by group, likely attributable to large differences in sample size. We incorporated robust standard error adjustments in our statistical model to accommodate these differences. By time eight, the sample size had decreased to less than 60 persons having COPD, the variability of means and width of confidence intervals increased. Data analysis was limited to seven events of time.

Regression analysis was used to investigate the hypothesis that functional performance mediates the relationship between cognition and life satisfaction. Separate mediation models examining domain-specific cognition (one per outcome e.g. executive function), functional performance by group (COPD, non-COPD) with life satisfaction were performed using Baron & Kenny's (1986) four step test for mediation. Three simple regressions were performed to determine if zero-order relationships existed among the variables. If there was no significance in one or more of these relationships it was concluded that mediation is not likely possible. Multiple regression was then performed. If causal relationship was no longer significant, then full mediation was supported. If the causal relationship was still significant but the regression coefficient declined, the findings supported partial mediation.

Multiple linear regression models were run to explore the impact of the psychosocial variables (perception of need for cognition, the sense of master, hopelessness and satisfaction with aging) on domain-specific cognition. One linear regression was run for each cognitive domain with the psychosocial variables as the predictor variables. We used semipartial correlations to explain the direction of the relationship and squared semiparital correlations to explain the unique contribution of each psychosocial variable on domain-specific cognitive measures.

Results

The sample size at baseline was 380 persons with COPD and 3070 non-COPD. There was no significant difference between groups (COPD and non-COPD) in age, gender or years of education. There were significant differences between the two groups on measures of sleep disturbance, marital status, and educational degrees. Characteristics of the sample population are presented in Table 1 (for more information see Table 1 Characteristics of Sample Population from the 2014 HRS Data Set). The sample size for the COPD Group decreased across the time of the study (for more information see Appendix Q: Table 21 Q. 1 Sample Size Based on Assessment Point).

Domains of cognition were compared between the two groups at baseline and 12 years later at the end of the study (time seven). There was a significant difference between groups in the cognitive domains of attention/executive function, and memory and learning. The differences remained significant from baseline to end of study except for immediate recall

Table 1: Characteristics of Sample Population from the 2014 HRS Data Set

	COPD N = 380 (11%)	Non-COPD N = 3070 (89%)	
	Mean (SD) Min/Max	Mean (SD) Min/Max	t-test, p-value
Age	75.89 (4.42) (65 - 89)	76.06 (4.41) (65 -89)	p = 0.47
Number of Years in School	12.20 (2.75) (0 - 17)	12.8 (3.05) (0 - 17)	p < 0.001
Sleep disturbance	2.21 (1.4)	1.94 (1.7)	p < 0.01
	Percentage (N)	Percentage (N)	χ^2, p - value
Gender Female Male	66.5 (253) 33.4 (127)	62.1(1907) 37.8(1163)	p = 0.09
Comorbidities	0 71.8 (273) 1 23.7 (90) 2 16 (21) 3 <0.001% (1)	0 85.8 (2637) 1 13.4 (86) 2 19 (21) 3 <0.001% (1)	p <0.001
Marital status Married Separate/Divorce Widowed Never married	 47.1 (179) 17.1 (65) 32.2 (123) 3.4 (13)	 60.7 (1866) 9.1 (304) 26.4 (814) 2.8 (68)	p <0.001
Education GED/left high school High School Some College Grad School	 26 (99) 46.3 (176) 13.6 (52) 13.9 (53)	 19.1 (589) 42.4 (1303) 13.8 (424) 24.6 (754) (24.6%)	p < 0.001
Smoking status Current Non-smokers Current smokers	 320 (84.25) 60 (15.7%)	 0	

The results are presented in Table 2 (for more information see Table 2: Cognitive Outcome Variables at Baseline and 12 years later from the HRS Data Set).

Change in cognition with the length of time with COPD.

Attention/Executive Function. Slopes declined significantly in both groups but the omnibus interaction between groups was not statistically significant χ^2 (6) = 4.85, p = 0.56. The

Table 2: Cognitive Outcome Variables at Baseline and 12 years later from the HRS Data Set

	COPD N = 380*		Non-COPD N = 3070*		
	Mean (SD)	Min/Max	Mean (SD)…	Min/Max	t-score p-value
Serial Sevens: Baseline	3.5 (1.4)	(1 – 5)	3.8 (1.4)	(0 – 5)	p <0.001
Serial Sevens: Year 12	3.1 (1.6)	(0 – 5)	3.7 (1.5)	(0 – 5)	p <0.001
Immediate Recall Baseline	5.4 (1.4)	(1 – 8)	6.3(1.5)	(0 – 10)	p <0.001
Immediate Recall Year 12	5.4 (1.5)	(2 – 10)	5.6(1.5)	(0 – 10)	p = 0.12
Delayed Recall Baseline	4.5 (1.7)	(0 – 7)	5.3 (1.9)	(0 – 10)	p <0.001
Delayed Recall Year 12	4.2 (1.7)	(0 – 10)	4.7 (1.8)	(0 – 10)	p <0.01

*Year 12: COPD N = 95 Non-COPD N = 3070

plot of means with 95% confidence intervals (CI) reveals rather parallel lines. (see Figure 14: Attention/Executive Function: Change in Mean over Time).

Memory & Learning. Slopes declined significantly in both groups. The omnibus interaction for immediate recall between the two groups was statistically significant (χ^2 (6) = 18.86, p = 0.004). The non-COPD group had a steeper decline than did the persons with COPD (see Figure 15 Memory and Learning: Immediate Recall Change in Means Over Time). Delayed recall, another measure of memory and learning, the slopes declined significantly in both groups but the omnibus interaction between groups was not significant (χ^2 (6) = 9.25, p = 0.016) (see Figure 16 Memory and Learning, Delayed Recall: Change in Mean Over Time).

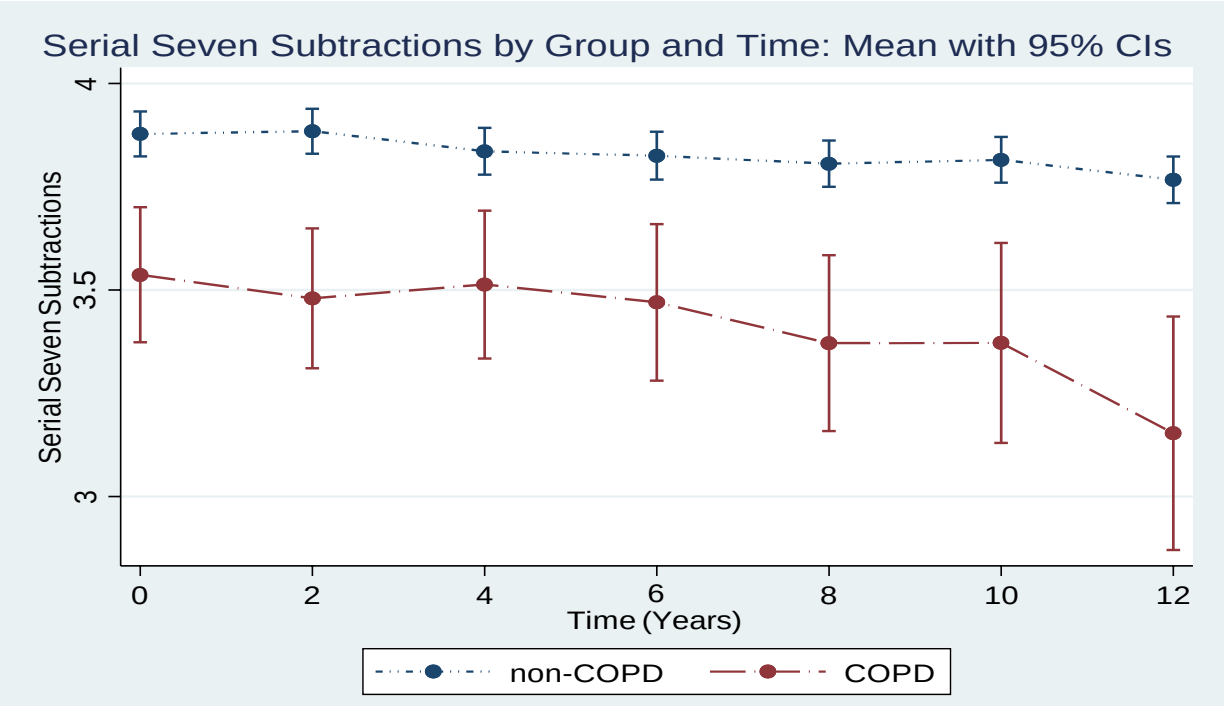


Figure 14 Attention/Executive Function: Change in Mean over Time

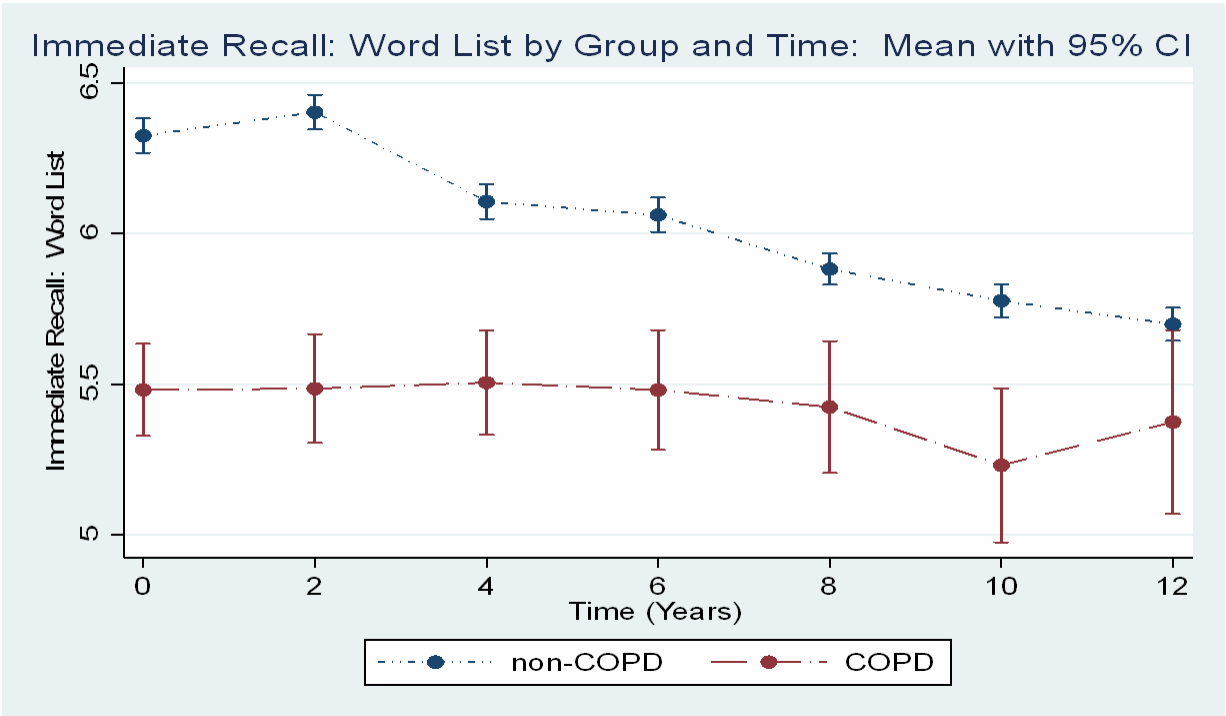


Figure 15 Memory and Learning, Immediate Recall Word List: Change in Mean over Time

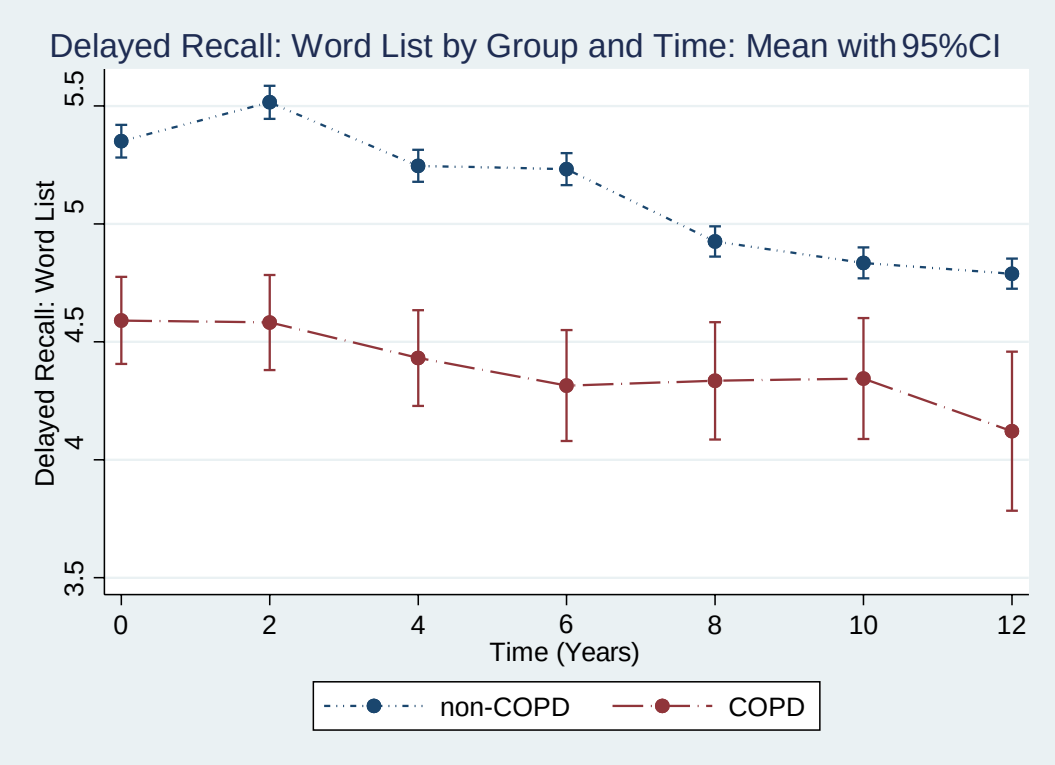


Figure 16: Memory and Learning Delayed Recall Word List: Change in Mean over Time

Impact of Domain Specific Cognition on Functional Performance

In a cross-sectional study, using 2014 wave of the HRS, the persons with COPD performed significantly worse on all measurements of functional performance; mobility, large muscle groups, gross motor skills and fine motor skills (for more information see Table 3: Comparison of Functional Performance Between Groups using Cross-sectional data in the 2014 Wave of the HRS Data Set).

Functional Performance as Mediator Between Domain-Specific Cognition (delayed recall) and Life Satisfaction

On the 5-point Likert scale of life satisfaction, there was no significant difference between the groups χ^2 (4) = 6.23, p = 0.182. In persons with COPD, there were no zero-order relationships between domains of cognition and life satisfaction: executive function (β = -0.038,

t (1) = -1.33 p = 0.185), memory and learning; immediate recall (β = -0.032, t (1) = -1.03 p = 0.303), delayed recall (β = -0.011, t (1) = -0.48 p = 0.06). Thus, there was no relationship to mediate. In the non- COPD group, a zero-order relationship was found between one measure in the domain of learning and memory. Delayed recall was a significant

Table 3: Comparison of Functional Performance Between Groups using Cross-Sectional data in 2014 Wave of HRS Data Set

	COPD N =380		Non-COPD N = 3070		
	Mean(SD)	Min/Max	Mean(SD)	Min/Max	t - score p-value
Mobility	1.5 (1.5)	0 - 5	0.41 (0.86)	0 – 5	p < 0.001
Large Muscle	1.7 (1.4)	0 - 4	.79 (1.14)	0 - 4	p < 0.001
Gross Motor Skills	0.62 (1)	0 – 5	0.12 (0.48)	0 - 3	p < 0.001
Fine Motor Skills	.20 (0.5)	0 - 3	0.05 (0.27)	1 - 5	p < 0.001

Higher Score indicates worse functional performance

predictor of life satisfaction (β = -0.018, t (1) = -2.40 p = 0.017), delayed recall was a significant predictor of functional performance (β = -0.317, t (1) = -10.31 p < 0.01). Delayed recall was no longer a significant predictor of life satisfaction after controlling for the mediator, functional performance, (β = -0.004, t (2) = -0.6, p = 0.95). These findings are consistent with full mediation. Approximately 3% of the variance in life satisfaction was accounted for by the predictors (R^2 = .03) (see Figure 17: Model Testing Relationship of Domain-Specific Cognition (Delayed Recall) and Life Satisfaction is Mediated by Functional performance in the non-COPD group).

Psychosocial Variables Impact on Domain-specific Cognition

There was no difference between the two groups in the perception of the need for cognition. The COPD group had statistically higher levels of hopelessness. The non-COPD group had a statistically higher sense of mastery, and satisfaction with aging (for more

information see Table 4: Cross- sectional Comparison of Differences in Psychosocial Variables by Groups in 2014 Wave of HRS Data set).

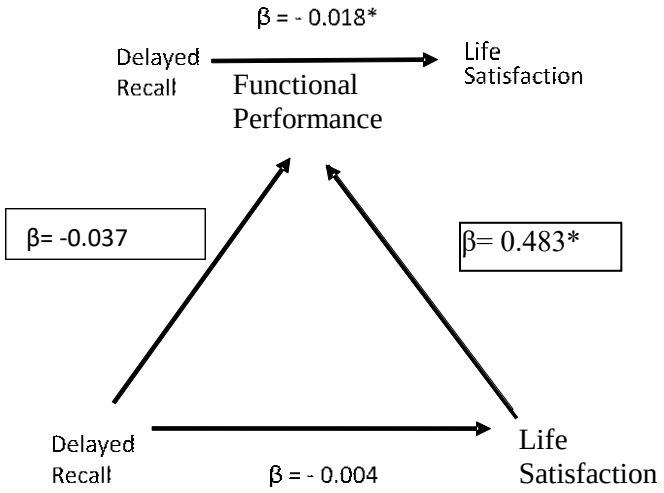


Figure 17 Model Testing Relationship of Domain-Specific Cognition (delayed recall) and Life Satisfaction is Mediated by Functional Performance in the non-COPD Group. Standardized regression coefficients and
**p<0.05.*

Table 4: Cross-sectional Comparison of Differences is Psychosocial Variables by Groups in 2014 Wave of the HRS Data Set

	COPD Mean (SD	Min/Max	Non-COPD Mean (SD)	Min/Max	p value
Need for cognition	N = 158 15.2 (3.0)	(5.1 – 23.8)	N = 1369 15.0 (3.1)	(5.1 - 25.8)	p = 0.33
Sense of Mastery	N = 161 18.9 (4.5)	(4.2 – 25.4)	N = 1433 20.2(4.2)	(4.2 – 25.2)	p < 0.001
Hopelessness	N = 159 8.2 (4.09)	(3.2 – 19.5)	N = 1413 7.38 (4.07)	(3.3 – 19.5)	p = 0.02
Satisfaction with Aging	N =162 25.4 (7.2)	(7.1 - 42.8)	N = 1409 28.6 (6.9)	(7.1 – 42.8)	p < 0.001

Number of respondents varies because of missing data. This portion of the HRS is from Psychosocial Leave Behind Survey that returned by mail

In the COPD group, the regression model for predictive values of the psychosocial

variables on attention/executive function was not significant (F (4,138) = 14.09, p = .226). The psychosocial variables explained 11% of the variance in immediate recall and 12% of the variance in delayed recall. In the non-COPD group, the psychological variables explained 3% of the variance in executive function, 4% of the variance in immediate recall and 4% of the variance in delayed recall (for more information see Appendix R: Table 22 R. 1 Regression of Psychosocial Variables on Domains of Cognition Cross-sectional Study from 2014 Wave of HRS Data Set).

The sense of mastery did not have a significant correlation with any of the domains of cognition in either group while hopelessness was significantly correlated with all domains in both groups (for more information see Table 5: Cross-sectional Comparison of Squared Semipartial Correlations between Cognition and Psychosocial Variables by groups in 2014 Wave of the HRS Data Set). In the COPD group, hopelessness was the only significant semipartial correlation. In the cognitive domain of memory and learning, immediate recall, the unique contribution of hopelessness was 7% and the unique contribution of delayed recall was 9% variance in the regression of psychosocial variables on cognition. In the non-COPD group, the need for cognition and satisfaction with aging was predicator of variance in every cognitive domain. Need for cognition unique contribution to variance was less than 1% in executive function, 7% in immediate recall and 3% in delayed recall. Satisfaction with aging explained 8% of variance in executive function, less than 1% in immediate and delayed recall.

Discussion

In this longitudinal study found that at baseline, the COPD group had significantly lower scores in executive function and learning and memory compared to the non-COPD group. When examining rate of change, there was no significant difference was found between the rate of change between the two groups in the domains of attention/executive function and delayed

recall. There was a significant difference in the rate of change in group having a sharper decline.

In examining the relationships between cognitive domains, functional performance and life satisfaction, in the COPD group, no zero-order relationships were established. We found

Table 5: Cross-sectional Comparison of Squared Semiparital Correlations between Cognition and Psychosocial Variable by Groups in 2014 Wave of the HRS Data Set

	1. Need for Cognition	2. Sense of Mastery	3. Hopelessness	4. Satisfaction with Aging
COPD				
Executive Function	$ry(1.2,3,4)^2$ 0.006 p = 0.35	$ry(2.1,3,4)^2$ 0.005 p = 0.39	$ry(3.1,2,4)^2$ 0.0080 p = 0.28	$ry(4.1,2,3)^2$ 0.0006 p = 0.77
Memory Immediate recall	$ry(1.2,3,4)^2$ 0.0112 P = 0.18	$ry(2.1,3,4)^2$ 0.0018 p = 0.60	$ry(3.1,2,4)^2$ 0.0701 p = 0.001	$ry(4.1,2,3)^2$ 0.0064 p = 0.31
Memory Delayed Recall	$ry(1.2,3,4)^2$ 0.0062 p = 0.32	$ry(2.1,3,4)^2$ 0.0004 p = 0.81	$ry(3.1,2,4)^2$ 0.0903 p = 0.0002	$ry(4.1,2,3)^2$ 0.0060 p = 0.3309
Non-COPD				
Executive Function	$ry(1.2,3,4)^2$ 0.0064 p = 0.003	$ry(2.1,3,4)^2$ 0.0011 p = 0.23	$ry(3.1,2,4)^2$ 0.0113 p = 0.0001	$ry(4.1,2,3)^2$ 0.002 p = 0.08
Memory Immediate recall	$ry(1.2,3,4)^2$ 0.0024 p = .07	$ry(2.1,3,4)^2$ 0.0016 p = 0.14	$ry(3.1,2,4)^2$ 0.0187 p = 0.00	$ry(4.1,2,3)^2$ 0.0052 p = 0.0081
Memory Delayed Recall	$ry(1.2,3,4)^2$ 0.0035 p = 0.03	$ry(2.1,3,4)^2$ 0.0007 p = 0.33	$ry(3.1,2,4)^2$ 0.0181 p = 0.00	$ry(4.1,2,3)^2$ 0.0037 p = 0.02

$ry(4.1,2,3)^2$ ⁻ indicates the correlation between cognitive variable and independent variable with the effects of the other variables removed from the first listed independent variable alone -squared semipartial regression.

in the non-COPD group, functional performance mediated the relationship between delayed recall and life satisfaction. Finally, the psychosocial variables, hopelessness was significant in both measures of memory in the COPD group and was significant across all domains in the non-COPD group. The need for cognition and satisfaction with aging, although they

explained only a small portion of the variance, were statistically significant for the non-COPD group only.

To our knowledge, this is the first longitudinal study that examined the change in domain-specific cognitive function over 12 years, comparing COPD and aged -matched non-COPD groups. The baseline findings showed that the COPD group performed lower on all measures of cognitive function compared to the non-COPD group. This finding is consistent with previous studies in which persons with COPD had lower scores across all domains of cognition at all ages (Dal Ben & Bricolo, 2012; Dal Negro et al, 2014). In addition, it supports findings that cognitive changes in COPD occur earlier in life than those in the non-COPD group. Current asymptomatic smokers, person with COPD or COPD requiring long term oxygen therapy were significantly impaired on tests of cognition (Clock Drawing, Trail Making Test A and B) in all ages of life with persons aged 40 – 59 having the most significant impairment (Dal Ben & Bricolo, 2012). In another study, the extent and prevalence of cognitive declines was greater in COPD subjects followed by chronic non-obstructive bronchitis and then asymptomatic smokers (Dal Negro et al., 2014). These finding indicate that the cognitive impairment may begin at the early stages of COPD. Many persons with COPD go undiagnosed until respiratory symptoms become problematic. In examining first time admissions for COPD exacerbations, it was found that 34% had undiagnosed COPD as defined by no self-report of COPD diagnosis and not on any medications to treat COPD (Balcells et al., 2015). These findings provide strong support for the notion that cognitive changes can occur prior to the diagnosis of COPD.

One plausible explanation for persons with COPD developing cognitive decline earlier in life than those without is based on theories of aging. Two prevalent theories of

aging are the programmed theory and the damage or error theory (Jin, 2012). In programmed theory, it implies that there is a timetable based on genetic expression that leads to deterioration over time. In the damage or error theory, the emphasis is on environmental assault that induces cumulative damage at various levels (Jin, 2012). Based on these theories, both groups would show decline based on the programmed theory of aging. However, persons with COPD would potentially have an earlier decline due to the cumulative assault that smoking has caused in the body.

Between the two groups, the only cognitive domain that had a significantly different rate of change over time was immediate recall. In immediate recall there was a significantly sharper decline for the non-COPD group. This may be explained by critical ages in life course of the brain. One critical age period for brain volume shrinkage occurs between the ages of 60-90 (Fjell et al., 2013). In cross-sectional analysis, the regions with the steepest estimated decline are the cerebral white matter and the hippocampus (Fjell et al., 2013). The shrinking volumes of cerebral white matter and hippocampus may relate to the age-related memory changes as white matter in the cerebral cortex is involved in the speed of processing information and the activation of the hippocampus for memory formation (Yanker, Lu & Loerch, 2008). The reason the sharp decline was not seen during the same time period in persons with COPD is that inflammation can accelerate the aging brain (p.57). We were able to partially support our hypothesis that there is a positive relationship between the length of time with COPD and declines in domain-specific cognition in persons with COPD.

Cognition has been identified as a predictor of life satisfaction. In a 3-year longitudinal study of the oldest old, persons aged 78 - 98-year-old, the cognitive domains of spatial abilities and processing speed predicted life satisfaction (Enkvist, Ekstrom, &

Elmstahl, 2013). In contrast, at baseline, we found no significant relationship between domain-specific cognition and life satisfaction in persons with COPD and only a weak relationship between delayed recall and life satisfaction in the non-COPD group. Life satisfaction levels have been found to stay consistent from late teens to early 70's and then decline steeply until the end of life (Baird, Lucas & Donnellan, 2010). A plausible explanation for the lack of a relationship between cognitive function and life satisfaction is the compensation of expectations and adjustment of personal goal to maintain a steady level of life satisfaction. As a person experiences age-related changes, they use strategies such as selection, optimization and compensation to maintain a level of life satisfaction (Baltes, 1997). Thus, we could not support our hypothesis the relationship between domain-specific and life satisfaction is mediated by functional performance.

Beyond age and disease, we examined four psychosocial variables that may impact domain-specific cognition; need for cognition, the sense of mastery, hopelessness and satisfaction with aging. Of these variables, hopelessness was a consistent significant predictor variable in both groups and in all domains of cognition except executive functions in persons with COPD. Although it was a significant predicator, the amount of variance that was predicted was different across groups. Two factors could explain the impact of hopelessness on cognitive function. The first is the stereotype embodiment theory. The stereotype embodiment theory, posits that age stereotypes are internalized across the lifespan and can influence functioning in old age when they become self-relevant (Levy, 2009). The process of internalizing stereotypes has two stages. In the first stage, a person develops expectations and trajectories of the aging process from external sources such as society and media, but it holds no relevance to them. The second stage occurs when the person

encounters elderly individuals in everyday life. From these two stages, negativity can be developed towards the aging process. Then, when the person reaches old age, this internalized stereotype can become a self-fulfilling prophecy (Levy, 2009). The hopelessness scale may have captured a portion of internalized stereotype and the fact that one knows that they cannot change the fact certain facts. Those with COPD know that the disease is not curable and in the non-COPD group they are aging and there is nothing that can be done about either.

The second factor that could explain the impact of hopelessness on cognition is depression. Depression is highly prevalent comorbidity in persons with COPD with estimated rates at approximately 40% compared to healthy elderly population that has estimated rate of 8 -16% (Fritzsche, et al., 2013). Depression influences cognition creating a bias that could have an impact on hopelessness. In depression, dysfunctional cognition and cognitive bias include recalling depression-specific stimuli better than positive or neutral stimuli, attention bias was found for depression-specific words and sad faces, and a limited ability to shift the focus of attention away from these stimuli (Fritzsche, et al., 2013). The focus on negative aspects could have an additive negative effect one's internalized stereotype.

Two other factors that explained a portion of the variance in cognition in the non-COPD group only were the need for cognition and satisfaction with aging. One plausible explanation for the difference in the need for cognition is education. Although there was not a significant difference in the years of education, there was a significant difference in degrees attained: 13.9% of COPD completed grad school compared to 24.6% in the non-COPD group. It is posited that the fact that persons attended college, they would have the tendency

for engaging in and enjoy thinking. A potential explanation for satisfaction with aging and its impact on cognition could also be related to having positive stereotypes regarding expectations of cognitive aging.

Results partially supported our hypotheses that the rate of change in domain-specific cognition is different between the two groups. Persons with COPD had significantly lower scores at baseline and at each time there was a further significant decline. Persons in the non-COPD group started with higher scores at baseline and had the sharpest decline in immediate recall. The results are consistent with findings from other studies. Studies suggest that cognitive changes occur earlier in life for persons with COPD and even before onset of COPD, the changes were seen in asymptomatic smokers (Dal Ben & Bricolo, 2014; Dal Negro et al., 2014). Future research on domain-specific cognition needs to incorporate younger persons with COPD.

In relationship between cognition and life satisfaction, no significant relationships were found in the COPD group. In the non-COPD group only one weak relationship was found. A weak relationship was found between delayed recall and life satisfaction, but it was fully mediated by functional performance. Further research is needed to better understand the relationship in persons with COPD.

Finally, we add to the body of literature a psychosocial aspect that explains some of the variance in cognition. The sense of hopelessness was a predictor of variance in all domains of cognition except executive future in the non-COPD. Hopelessness was a strong predictor of the variance in immediate and delayed recalls in the COPD group and a weak predicator of variance all domains in the non-COPD group. Additionally, the need for cognition and satisfaction with aging were weak predictors of cognition in the non-COPD

group. Further research is needed in examining the impact of hopelessness on cognition in persons with COPD.

Strengths of the study was a population-based nationally representative, biennial longitudinal health survey began in 1992. We had a large sample size and were able to follow persons for 14 years. Limitations to this study are the cognitive assessments used and not a state of the art cognitive battery but were the cognitive tests that were available in the data base for a secondary analysis and are reasonable given the mode administration. Also present in the study was survivor effect. By selecting persons that were alive in 2014 and then searching back in time for first report, but we may have missed data from those that did not survive to the first data point.

In this study, persons with COPD had poorer performance in all cognitive domains at baseline. Although both groups had a significant decline in all domains of cognition, the non-COPD groups had the sharpest decline occurring in the domain of immediate memory. The relationships between domains of cognition and life satisfaction and social participation and life satisfaction were weak and only present in the non-COPD group. The relationship between delayed recall and life satisfaction was fully mediated by functional performance. Each cognitive domain partially mediated the relationship between social participation and life satisfaction. Hopelessness was a significant predicator of memory and learning across both groups while need for cognition and satisfaction with aging was a weak predictor of cognition in all domains in the non-COPD group. Further research needs to examine the dynamic interactions between domain-specific cognition, functional performance, and life satisfaction.

BIBLIOGRAPHY

Baird, B., Lucas, R., & Donnellan, M. (2010). Life Satisfaction Across the Lifespan: Findings from Two Nationally Representative Panel Studies. *Soc Indic Res, 99*(2), 183-203. http://dx.doi.org/doi:10.1007/s11205-010-9584-9

Balcalls, E., Gimeno-Santos, E., de Batlle, J., Ramon, M., Rodriguez, E., Benet, M., . . . Group., P.-C. s. (2015). Characterization and prognosis of undiagnosed chronic obstructive pulmonary disease patients at their first hospitalization. *BMC Pulmonary Medicine, 15*(4).

Baltes, P. B. (1997). On the Incomplete Architecture of Human Ontogeny Selection, Optimization, and Compensation as Foundation of Developmental Theory. *American Psychologist, 52*(4), 366-380.

Bandura, A. (1977). Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev, 84*(2), 191-215.

Baron, R., & Kenny, D. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*(6), 1173-1182. http://dx.doi.org/10.1037/0022-3514.51.6.1173

Cacioppo, J., Petty, R., & Kao, C. (1984). The efficient assessment of need for cognition. *J Pers Assess, 48*(3), 306-307. http://doi.dox.org/10.1207/s15327752jpa4803_13

Cleutjens, F. A., Spruit, M. A., Ponds, R. W., Dijkstra, J. B., Franssen, F. M., Wouters, E. F., & Janssen, D. J. (2014). Cognitive functioning in obstructive lung disease: results from the United Kingdom biobank. *J Am Med Dir Assoc, 15*(3), 214-219. http://dx.doi.org/10.1016/j.jamda.2013.12.007

Cleutjens, F. A., Franssen, F. M., Spruit, M. A., Vanfleteren, L., Gijsen, C., Dijkstra, J. B., . . . Janssen, D. J. (2017). Domain-specific cognitive impairment in patients with COPD and control subjects. *International Journal of Chronic Obstructive Pulmonary Disease, 12*, 1-11. http://dx.doi.org./10.2147/COPD.S119633

Colcombe, S., & Kramer, A. (2003). Fitness Effects on the Cognitive Function of Older Adults. *Psychological Science, 14*(2), 125-130.

Crisan, A. F., Oancea, C., Timar, B., Fira-Mladinescu, O., Crisan, A., & Tudorache, V. (2014). Cognitive impairment in chronic obstructive pulmonary disease. *PLoS ONE, 9*(7), e102468. http://dx.doi.org/10.1371/journal.pone.0102468

Dal Ben, S., & Bricolo, F. P. (2012). The Psychological and Cognitive Profile. In R. W. Dal Negro & R. Hodder (Eds.), *Long-Term Oxygen Therapy: new insight and perspectives* Milan, Italia: Springer.

Dal Negro, R. W., Bonadiman, L., Tognella, S., Bricolo, F. P., & Turco, P. (2014). Extent and prevalence of cognitive dysfunction in chronic obstructive pulmonary disease, chronic non-obstructive bronchitis, and in asymptomatic smokers, compared to normal reference values. *Int J Chron Obstruct Pulmon Dis, 9*, 675-683. http://dx.doi.org10.2147/COPD.S63485

Daniel, M., Brown, A., Dhurrkay, J., Cargo, M., & O'Dea, K. (2006). Mastery, perceived stress and health-related behaviour in northeast Arnhem Land: a cross-sectional study. *International Journal for Equity in Health, 5*(10). http://dx.doi.org10.1186/1475-9276-5-10

Dodd, J. W., Getov, S. V., & Jones, P. W. (2010). Cognitive function in COPD. *Eur Respir J, 35*, 913- 922. http://dx.doi.org/10.1183/09031936.00125109

Dodd, J. W., Charlton, R., van den Broek, M., & Jones, P. W. (2013). Cognitive Dysfunction in Patients Hospitalized with Acute Exacerbation of COPD. *CHEST, 144*(1), 119-127.

Eisner, M., Iribarren, C., Blanc, P., Yelin, E., Ackerson, L., Byl, N., . . . Katz, P. (2011). Development of disability in chronic obstructive pulmonary disease: beyond lung function. . *Thorax, 66*, 108-114. http://dx.doi.org10.1136/thx.2010.137661

Enkvist, A., Ekstrom, H., & Elmstahl, S. (2013). Associations between cognitive abilities and life satisfaction in the oldest-old. Results from the longitudinal population study Good Aging in Skane. *Clinical Interventions in Aging, 8*, 845-853. http://dx.doi.org/10.2147/CIA.545382

Favalli, A., Miozzo, A., Cossi, S., & Marengoni, A. (2008). Differences in neuropsychological profile between healthy and COPD older persons. *Int J Geriatr Psychiatry, 23*(2), 220-221. http://dx.doi.org/10.1002/gps.1847

Ferrans, C., Zerwic, J., Wilbur, J., & Larson, J. (2005). Conceptual Model of Health-Related Quality of Life. *Journal of Nursing Scholarship, 37*(4), 336-342.

Fioravanti, M., Nacca, D., Amati, S., Buckley, A., & Bisetti, A. (1995). Chronic Obstructive Pulmonary Disease and Associated Patterns of Memory Decline. *Dementia, 6*, 39-48. Fjell, A., Westlye, L., Grydeland, H., Amlien, I., Espeseth, T., Reinvang, I., . . . Initiative., t. A. D. N. (2013). Critical ages in the life course of the adult brain: nonlinear subcortical aging. *Neurobiology of Aging, 34*, 2239-2247. http://dx.doi.org/10.1016/j.neurobiolaging.2013.04.006

Fritzche, A., Watz, H., Magnusen, H., Tuinmann, G., Lowe, B., & von Leupoldt, A. (2013). Cognitive biases in patients with chronic obstructive pulmonary disease and depression – a pilot study. *British Journal of Health Psychology, 18*, 827-843. http://dx.doi.org/10.1111/bjhp.12025

Grant, I., Heaton, R., McSweeny, J., Adams, K., & Timms, R. (1982). Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease. *Arh Intern Med, 142*, 1470-1476.

Håkansson, K., Soininen , H., Winblad, B., & Kivipelto, M. (2015). Feelings of Hopelessness in Midlife and Cognitive Health in Later Life: A Prospective Population-Based Cohort Study. *PLoS ONE*. doi:DOI:10.1371/journal.pone.0140261

Hung, W., Wisnivesky, J., Siu A., & Ross, J. (2009). Cognitive Decline among Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory Critical Care Medicine, 180,* 134-137. http://dx.doi.org10.1164/rccm.200902-0276OC

Herzog, R., & Wallace, R. (1997). Measures of Cognitive Functioning in the AHEAD Study. *The Journals of Gerontology, 52B* (Special Issue), 37-48.

Hung, W., Wisnivesky, J., Siu A., & Ross, J. (2009). Cognitive Decline among Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory Critical Care Medicine, 180*, 134-137. http://dx.doi.org/10.1164/rccm.200902-0276OC

Incalzi, R. A., Gemma, A., Marra, C., Muzzolon, R., Capparella, O., & Carbonin, P. (1993). Chronic Obstructive Pulmonary Disease: An Original Model of Cognitive Decline. *Am Re Respir Dis, 148*, 418-424.

Incalzi, R. A., Gemma, A., Marra, C., Capparella, O., Fuso, L., & Carbonin, P. (1997). Verbal Memory Impairment in COPD: Its Mechanisms and Clinical Relevance. *CHEST, 112*, 1506-1513.

Incalzi, R. A., Bellia, V., Maggi. S., Imperiale, C., Capparella, O., Catalano, R., Carbonin, P., Rengo, F., & the Sa.R.A. (Salute Respiratoria nell'Anziano) Study Group. (2002). Mild to moderate chronic airways disease does not carry an excess risk of cognitive dysfunction. *Aging Clin Exp Res, 14*(5), 395-401.

Jin, K. (2010). Modern Biological Theories of Aging. *Aging and Disease, 1*(2), 72-74.

Kanno, S., Saito, M., Hayashi, A., Uchiyama, M., Hiraoka, K., Nishio, Y., . . . Mori, E. (2012). Counting- backward test for executive function in idiopathic normal pressure hydrocephalus. *Acta Neurologica Scandinavica, 126*, 279-286. http://dx.doi.org/10.111/j.1600-0404.2012.01644.x

Kapella, M., Larson, J., Covey, M., & Alex, C. (2011). Functional Performance in Chronic Obstructive Pulmonary Disease Declines with Time. *Med Sci Sports Exerc, 43*(2), 2118-2224. http://dx.doi.org//10.1249/MSS.0b013e3181eb6024

Karzmark, P. (2000). Validity of Serial Sevens. *International journal of Geriatric Psychiatry, 15*, 677- 679.

Katz, P., Gregorich, S., Eisner, M., Julian, L., Chen, H., Yelin, E., & Blanc, P. (2010). Disability in Valued Life Activities among Individuals with COPD ad Other Respiratory Conditions. *J Cardiopulm Rehabil Prev, 30*(2), 126-136. http://dx.doi.org/10.1097/HCR.0b013e3181be7e59

Krop, H., Block, J., & Cohen, E. (1973). Neuropsychologic Effects of Continuous Oxygen Therapy in Chronic Obstructive Pulmonary Disease*. *CHEST, 64*(3), 318-322.

Lachman, M., & Andreoletti, C. (2006). Strategy use mediates the relationship between control beliefs and memory performance for middle-aged and older adults. *J Gerontol B Psychol Sci Soc Sci, 61*(2), P88-94.

Lee, W., & Kim, S. (2014). Effects of Achievement Goals on Challenge Seeking and Feedback Processing: Behavioral and fMRI Evidence. *PloS Medicine, 9*(9). http://dx.doi.org/10.1371/journal.pone.0107254

Leidy, N. (1994). Functional status and the forward progress of merry-go-rounds: toward a coherent analytical framework. *Nur Res, 43*(4), 196-202

Levy, B., Slade, M., & Kasl, S. (2002). Longitudinal Benefit of Positive Self-Perceptions of Aging on Functional Health. *Psychological Science, 57B*(5), 409-417.

Levy, B., & Leifheit-Limson, E. (2009). The Stereotype-Matching Effect: Greater Influence on Functioning When Age Stereotypes Correspond to Outcomes. *Psychology and Aging, 24*(1), 230- 233. http://dx.doi.org/10.1037/a0014563

Martinez, C., Richardson, C., Han, M., & Cigolle, C. (2014). Chronic Obstructive Pulmonary Disease, Cognitive Impairment and Development of Disability: The Health Retirement Study. *Annals ATS, 11*(9), 1362-1370. http://dx.doi.org/10.1513/AnnalsATS.20145-187OC

Pavot, W., Diener, E., Colvin, R., & Sandvik, E. (1991). Further Validation of the Satisfaction with Life Scale: Evidence for the Cross-Method Convergence of Well-Being Measures. *Journal of Personality Assessment, 57*(1), 149-161.

Pompili, M., Innamorati, M., Gonda, Z., Serafini, G., Sarno, S., Erbuto, D., . . . Girardi, P. (2013).Affective temperaments and hopelessness as predictors of health and social functioning in mood disorder patients: A prospective follow-up study. . *Journal of Affective Disorders, 150*(216-222). http://dx.doi.org/10.1016/j.jad.2013.03.026

Prigatano, G. P., Parsons, O., Levin, D., Wright, E., & Hawryluk, G. (1983). Neuropsychological Test Performance in Mildly Hypoxic Patients with Chronic Obstructive Pulmonary Disease. *Journal of Consulting and Clinical Psychology, 51*(1), 108-116.

Radloff, L. (1977). The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measures, 1*(3), 385-401.

Singh, B., Mielke, M., Parsaik, A., Cha, R., Roberts, R., Scanion, P., . . . Peterson, R. (2014). A Prospective Study of Chronic Obstructive Pulmonary Disease and the Risk for Mild Cognitive Impairment. *JAMA Neurol, 71*(5), 581-588. http://dx.doi.org./10.001/jamaneurol.2014.94

Smith, J., Ryan, L., Fisher, G., Sonnega, A., & Weir, D. (2017). Psychosocial and Lifestyle Questionnaire 2006 - 2016: Documentation Report. Retrieved https://hrs.isr.umich.edu/sites/default/files/biblio/HRS%202006-2016%20SAQ%20Documentation_07.06.17.pdf

STATA: StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC

Strauss, E., Sherman, E., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests: ADMINISTRATION, NORMS and COMMENTARY*. New York, New York.: Oxford University Press.

Thakur, N., Blanc,P., Julian L., Yelin, E., Katz, P, Sidney, S., Iribarren, C., & Eisner, M. (2010). COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. *International Journal of Chronic Obstructive Pulmonary Disease, 5*, 263-269.

Voyer, P., Champoux, N., Desrosiers, J., Landreville, P., Monette, J., Savoie, M., . . . Bedard, (2006). Assessment of inattention in the context of delirium screening: one size does not fit all! *International Psychogeriatrics, 28*(8), 1293-1301. http://dx.doi.org/10.1017S10416110216000533

Weissman, M., Sholomskas, D., Pottenger, M., Prusoff, B., & Locke, B. (1977). Assessing Depressive Symptoms in Five Psychiatric Populations: A Validation Study. *American Journal of Epidemiology, 106*(3), 203-214.

Yanker, B., Lu, T., & Loerch, P. (2008). The Aging Brain. *Annu Rev Pathol Mech Dis, 3*, 41-46. http://dx.doi.org/10.1146/annurev.pathmechdis.2.010506.092044

CHAPTER IV

Assessing Domain-specific Cognition in Persons with Mild to Severe COPD: Feasibility and Acceptability of Computerized Adaptive Testing

COPD is one of the major causes of disability among middle-aged adults in the U.S. Persons with COPD have a 10-fold higher risk of developing disability than members of the general population (Eisner et al., 2011). Beyond the impact on the pulmonary system, COPD has extrapulmonary effects which influence the quality of life. Extrapulmonary features of COPD include weight loss, decrease in muscle mass, decrease in strength and endurance, osteoporosis, heart failure, anxiety, depression and cognitive impairment (Cleutjens, Janssen, Ponds, Dijkstra, & Wouters, 2014). The focus of this research was domain-specific cognition, functional performance and life satisfaction.

There is strong evidence that persons with COPD have increased risk and higher prevalence of cognitive decline both in global measures and domain-specific measures of cognition. Studies have shown that persons with COPD are at an increased risk and have a higher incidence of global cognitive decline (Hung, Wisnivesky, Siu, & Ross, 2009; Martinez, Richardson, Han, & Cigolle et al., 2014; Ozge, Ozge, & Unal, 2006; Singh et al., 2014; Thakur et al., 2010). Persons with COPD also have significantly poorer performance in the domain-specific cognition. Significant differences were found in the domains of attention (Grant, Heaton, McSweeny, Adams, & Timms, 1982), short-term memory (Cleutjens et al., 2014; Favali et al., 2008; Fioravanti, Nacca, Amati, Buckley & Bisetti, 1995; Incalzi et al., 1999), long-term memory (Cleutjens et al., 2014, Favalli et al., 2008;

Incalzi et al., 1997), language (Favalli, et al., 2008) and processing speed (Cleutjens et al., 2014). These results suggest that both global and domain-specific cognition are compromised in persons with COPD.

There is a small body of evidence that supports view that a decline in cognition contributes to functional decline. Using measures of global cognition many studies have found an association between cognitive decline and decreased functional performance in persons with COPD (Antonelli-Incalzi et al., 2008; Feng, Lim, Collinson, & Ng, 2012; Ozge et al., 2006). In a two-year longitudinal study, cognitive impairment had an additive effect on disability that occurs in person with COPD (Martinez et al., 2014). Antonelli-Incalzi et al. (2008) observed cognitively lower function persons with COPD had higher prevalence in dependence in ADLs and IADLs. Cognitive decline and decreased functional performance have been associated with a decline in life satisfaction (Blinderman, Homel, Billings, Tennstedt, & Portenoy, 2009). In addition to the basic activities needed for survival, declines also occur in valued life activities. Valued life activities are those activities that are important to the individual. As a person experiences loss in functional performance, preserving energy for activities needed for survival, there a greater reduction in valued life activities (Katz et al., 2010). The performance of the valued activities is closely more closely linked to life satisfaction than are activities of survival (Katz et al., 2010). Even though there is a link between cognitive decline, functional performance and life satisfaction, the evidence supporting the link is weak. Further research that examines the relationship levels of functional performance and life satisfaction is needed.

The purpose of this research was to examine the relationships between domain-specific cognition and other related factors, functional performance, and life satisfaction. To

depict the relationships for this study a second modified visual representation of the interactions between Cognition, Functional Performance, and Life Satisfaction was created (see Figure 18: Second Modified Visual Representation of Relationships Among Cognition, Functional Performance, and Life Satisfaction with inclusion of PROMIS and NIHTB-CB variables). This work was guided by two frameworks: Revised Cleary & Wilson Model of Health-Related Quality of Life (Ferrans et al., 2005) (see Appendix A for more information on Revised Cleary & Wilson Model of Health-Related Quality of Life) and Functional Status Framework (Leidy, 1994). The revised Cleary & Wilson Model of Health-Related Quality of Life illustrates the dynamic interactions between health, functioning, and life satisfaction (Ferrans et al., 2005). The Functional Status Framework defines functional performance as "those activities that people do in the normal course of their lives to meet basic needs and fulfill usual roles and maintain health and well- being" (Leidy, 1994, p. 197.). It also describes characteristics of the individual that may influence functional performance including cognition, emotional states of anxiety and depression, and sleep disturbances (Leidy, 1994). Life satisfaction is subjective well-being related to how happy or satisfied someone is with various aspects of their lives (Ferrans et al., 2005).

Several factors have made it difficult to describe the pattern of domain-specific cognitive decline. One issue is the lack of an accepted universal classification of cognitive domains (Dodd et al., 2010, p.914). In a review of 16 articles, Torres-Sanchez et al. (2015) found that 39 neuropsychological tests were used to assess seven cognition domains. Presently, there is no standard assessment tool to evaluate global cognition, and there is no standard for the types or number of neuropsychological tests required for evaluation of

domains of cognition. The use of different tools to assess the same cognitive function has made it difficult to compare data across studies.

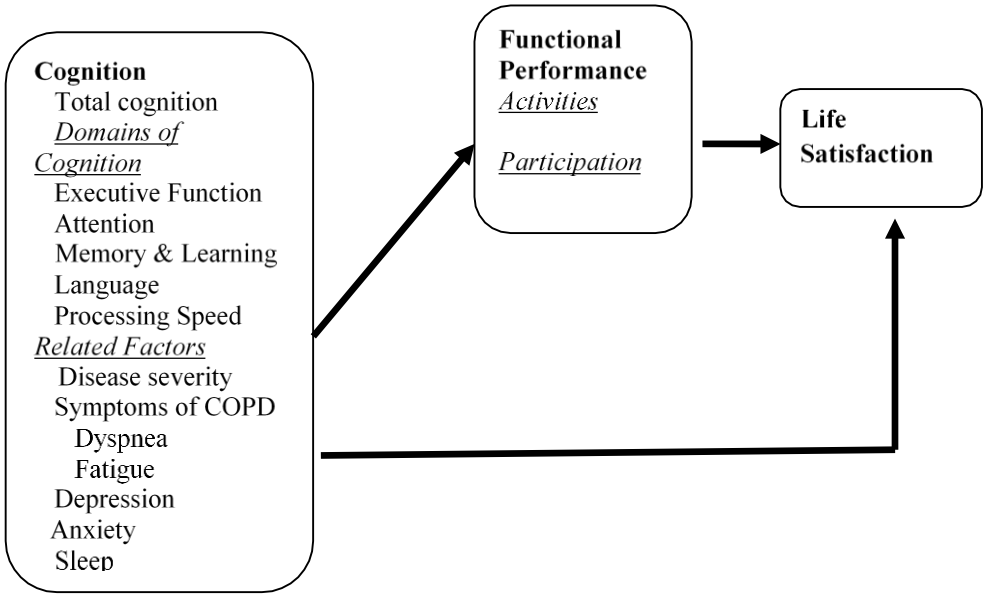


Figure 18: Second Modified Visual Representation of Relationship among Cognition, Functional Performance and Life Satisfaction with inclusion of PROMIS and NIHTB-CB Variables

It is important to assess cognition using a standard battery. There are many studies that have collected data on aspects of cognitive decline in persons with COPD. However, little uniformity was found in assessing the various domains of cognitive function (Torrez-Sanchez et al., 2015). Noting that the lack of standardized measures made it difficult to compare and interpret findings across studies and populations, NIH awarded contracts to develop standardized tests meet the need of enhancing comparison of results across studies and to be used in data collection in large cohort studies (Talan, 2012). Two batteries of instruments were created; patient reported outcome measurement information system (PROMIS®) and the National Institute of Health (NIH) Toolbox® (NIHTB). PROMIS® assesses many patient-reported outcomes including pain, fatigue, emotional distress, physical

functioning and social role participation (Cella et al., 2010). The NIHTB divides tests into four aspects of neural function called cognition, sensation, motor, and emotion. The NIHTB cognition battery (NIHTB-CB) is further divided into cognitive domains and currently consists of seven test instruments to measure abilities within the five major domains (Heaton et al., 2014). The need for a "state-of-the-art" instrument which was brief, less than 30 minutes led to the use of the digital platform.

To our knowledge, the NIHTB-CB has not been used to measure cognitive function in persons with COPD. The primary aim of this research is to determine the feasibility and acceptability of using computer adaptive testing tools from the NIHTB-CB for assessment of domain-specific cognition in persons with COPD. A secondary aim is to describe a preliminary estimate of the strength of the relationship among domain-specific cognition, functional performance and life satisfaction in persons with mild to severe COPD.

Methods

Nineteen participants were recruited from pulmonary clinics at the University of Michigan Health System and by referral. Inclusion criteria were over the age of 55, documented FEV_1, ability to walk and to take computerized tests. Exclusion criteria include impairment, taking Aricept or Namenda, taking any medications that would alter cognition or history of a stroke.

To our knowledge, the NIHTB-CB has not been used to measure cognitive function in persons with COPD. The primary aim of this research is to determine the feasibility and acceptability of using computer adaptive testing tools from the NIHTB-CB for assessment of domain-specific cognition in persons with COPD. A secondary aim is to describe a

preliminary estimate of the strength of the relationship among domain-specific cognition, functional performance and life satisfaction in persons with mild to severe COPD.

PROMIS® CAT and NIHTB-CB Measurements

PROMIS® is available via paper questionnaire, interactive voice response or computer adaptive testing (CAT). According to Bjorner et al. (2014), there were no statistically or clinically significant differences in scores or psychometric properties between the three methods of administration. The basis of PROMIS® CAT is item response theory (HealthMeasures, 2017). Each assessment lasts approximately one minute. The person receives items until they reach a specified level of measurement precision or a specific number of items, usually 4 - 12. In a study of persons with multiple sclerosis, persons took the PROMIS® CAT surveys in 4.08 minutes while the estimated completion time with paper and pencil test was estimated at 15.6 minutes (Senders, Hanes, Bourdette, & Shinto, 2015).

NIHTB-CB is a set of brief psychometrically sound instruments to assess motor, emotional, sensory and cognitive function in the person aged 3 – 85 (NIHTB, 2015). Survey data from 102 cognitive experts was used to select NIHTB-CB domains. The cognitive experts endorsed Executive Function (95%), Episodic Memory (93%), Language (55%), Processing Speed (52%) and Attention (50%) and 57% indicated that a "Global Score" would be desirable (Weintraub et al., 2014).

Measurements selected from PROMIS® are based on related factors of cognition from the visual representation. All seven instruments from the NIHTB-CB assessing the five domains of cognition were included in this study (for more information see Table 6: List of Variables and Measures used from PROMIS® CAT and NIHTB-CB).

Table 6 List of Variables and the Measures used from PROMIS CAT Test and NIHTB-CB

Variable	**PROMIS® CAT test**	**NIHTB-CB**
Disease Severity	NA	NA
Dyspnea	NA	NA
Fatigue	Fatigue	
Sleep	Sleep Disturbance	
Emotional State	Anxiety Depression	
Cognition Attention Executive Function Episodic Memory Language Processing Speed Working Memory		NIH Toolbox Flanker Inhibitory Control and Attention Test NIH Toolbox Dimension Change Card Sort Test NIH Toolbox Picture Sequence Memory Test NIH Toolbox Picture Vocabulary and NIH Toolbox Oral Reading Recognition Test NIH Toolbox Pattern Comparison. NIH Toolbox Oral Reading Recognition Test
Functional Performance	Physical Function Mobility Ability to Participate Social	
Life Satisfaction		General Life Satisfaction Survey

The select of this content does not necessarily represent an endorsement by the US Federal Government or PROMIS®. See www.nihPROMIS® .org for additional information on the PROMIS® Initiative.

Domain-specific Cognition

The NIHTB-CB has been normed and validated across the lifespan in subjects ages 3-85. Convergent and discriminant validity measures have been performed on all NIH toolbox measures (for more information see Appendix S: Table 23 S. 1 Convergent and Discriminant Validity of the NIHTB-CB Persons Aged 8 - 85 and Appendix T: Table 24 Reliability of NIHTB-CB).

Attention and Executive Function. NIH Toolbox Flanker Inhibitory Control and Attention Test and NIH Toolbox Dimension Change Card Sort Test were used to assess executive function. In the Flanker test, the participant must focus on a given stimuli while inhibiting attention to stimuli flanking it. The participant is presented with a series of five arrows and must select the direction of the middle arrow. The test takes approximately four minutes to administer. Convergent validity $r = -0.48$, $p < 0.001$, discriminant validity $r = 0.15$, $p < 0.001$ and reliability $r = 0.85$. The Dimensional Change Card Sort Test measures flexibility and attention. The participant is given two pictures with two dimensions, shape and color. The participant must select the appropriate dimension based on a word displayed in the center of the screen. The test takes about four minutes to administer. Convergent validity $r = -0.51$, $p < 0.001$, discriminant validity $r = 0.14$, $p < 0.05$ and reliability $r = 0.88$.

Episodic memory. NIH Toolbox Picture Sequence Memory Test assessed episodic memory. As a sequence of pictures appears in the center of the screen, a recording describes it. The computer places the picture in a fixed order around the border of the screen. Once all the pictures are in place, they return to the center of the screen. The participant must return the pictures to their proper place. The test takes about ten minutes to administer. Convergent validity $r = 0.69$, $p < 0.001$, discriminant validity $r = -0.08$, $p < 0.05$ and reliability $r = 0.77$ (Weintraub et al., 2014).

Language. Language was measured with the NIH Toolbox Picture Vocabulary. The Picture Vocabulary Test measures receptive vocabulary. The participant is read a word and has four pictures on the screen and must select the picture that best matches the word provided. The test takes about five minutes to administer. Convergent validity $r = 0.78$, $p < 0.001$, discriminant validity $r = -0.08$, $p < 0.05$ and reliability $r = 0.81$ (Weintraub et al., 2014). The NIH Toolbox Oral Reading Recognition Test is a single word reading task that has been used to estimate the quality of education. The test takes about four minutes to administer. Convergent validity $r = 0.93$, $p < 0.001$, discriminant validity $r = -0.19$, $p < 0.001$ and reliability $r = 0.77$ (Weintraub et al., 2014).

Processing Speed. Processing Speed was assessed using the NIH Toolbox Pattern Comparison. The participant is asked to compare two pictures presented side by side to determine if they are the same or different. They are given 85 seconds to respond to as many pairs of pictures as possible. The test takes about three minutes to administer. Convergent validity $r = 0.49$, $p < 0.001$, discriminant validity $r = 0.12$, $p < 0.05$ and reliability $r = 0.72$ (Weintraub et al., 2014).

Working memory. Working memory was assessed using the NIH Toolbox Oral Reading Recognition Test. The participant is presented with visual and verbal lists. The participant is then asked to sort and recall the list. For example, the participant is given three animals and must state them back in order of smallest to largest. The test takes about seven minutes to administer. Convergent validity $r = 0.58$, $p < 0.001$, discriminant validity $r = 0.30$, $p < 0.001$ and reliability $r = 0.77$(Weintraub et al., 2014).

Composite Scores of Crystallized, Fluid and Cognitive Function

Fluid Cognition Composite Score. This composite score includes all the tests noted above that reflect fluid ability: Flanker, Dimensional Change Card Sort, Picture Sequence Memory, List Sorting and Pattern Comparison. Fluid abilities are used to problem solve, respond quickly to stimuli, and encode new episode memories. Fluid abilities are essential in adapting to new situations in everyday life. They are more sensitive to neurobiological integrity including changes with aging or systemic disorders that alter brain function (Toolbox Scoring).

Crystallized Cognition Composite Score. The composite score is the average of the scores from the Picture vocabulary and Reading Tests. Crystallized abilities are presumed to be more dependent on experience and less on biological influences. Experience heavily influences crystallized cognition composite score as it represents an accumulated store of verbal knowledge and skills and thus are heavily influenced by education (Toolbox Scoring).

Cognitive Function Composite Score. The Cognitive Function Composite is the average of the Fluid and Crystallized composites. Interpretation is like a "full-scale score." It provides a highly reliable overall snapshot of general cognitive functioning (Toolbox Scoring). The test-retest reliability of the composite scores were acceptable; crystallized r = .85, fluid r = .76 and total cognition r = .88 (Akshoomoff et al., 2013). Convergent validity of the composite scores for age 8-85 were crystallized r =.90 (df =85), fluid r = .70 (df = 85) and total r = .88 (df =113); all p values were < .0001 (Akshoomoff et al, 2013, p.15).

Related factors

Disease severity. Disease severity was determined by using the GOLD COPD staging system (for more information see Appendix B: Table 10 B.1 GOLD COPD staging system) which includes predicted FEV_1% based on age, gender, height, weight, the impact of the

disease on well-being and daily life The GOLD COLD staging systems has a combined assessment which adds risks of exacerbation and symptoms to the classification system. Exacerbations are assessed by examining the numbers of exacerbations per year and determining whether the exacerbation led to hospitalization. Degrees of symptoms are determined by using the COPD Assessment Test (for more information see Appendix C: COPD Assessment Test) and the modified Medical Research Council (mMRC) dyspnea scale (for more information see Appendix D the mMRC dyspnea scale). The results are then calculated using the combined assessment tool (for more information see Appendix E: Table 11 E. 1 Combined Assessment Tool of COPD).

Symptoms of COPD. Dyspnea was measured with mMRC dyspnea scale. Fatigue was measured with the PROMIS CAT fatigue scale.

Dyspnea. Dyspnea was assessed using the modified Medical Research Council (mMRC) dyspnea scale (for more information see Appendix D the mMRC dyspnea scale). The mMRC is a simple and valid method of categorizing patients with COPD in terms of their disability based on breathlessness. Intraclass correlation coefficient for test-retest reliability at a 6 $\pm$ 5-day interval was 0.82 with 95% CI (0.72-0.88) (Mahler et al., 2009). It was found that the mMRC detected changes between stages II & IV and III & IV but not between II & III (Mahler et al., 2009).

Fatigue. Fatigue was measured using the PROMIS® Fatigue CAT instrument. The instrument measures fatigue from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion (HealthMeasures, 2017). Four items must be completed to receive a T score. A higher score indicates more fatigue (HealthMeasures, 2014). Reliability of the PROMIS® fatigue short form was .88 across samples in healthy controls, and its correlations with scores on the Multidimensional Fatigue Symptom Inventory-Short Form and Brief Fatigue Inventory was .60 to .85 (Ameringer et al., 2016).

Emotional State

Depression. Depression was measured using the PROMIS® CAT depression scale. The PROMIS® depression scale assesses negative mood, negative views of self, negative social cognition, and decreased positive affect and engagement (PROMIS®). The internal reliability of all scales for depression had a Cronbach's alpha 0.93 (Kroenke, Yu, Wu, Kean, & Monahan, 2014).

Anxiety. Anxiety was measured using the PROMIS® CAT Anxiety Scale The PROMIS® Anxiety scale assesses fear, anxious misery, hyperarousal, and somatic complaints related to hyperarousal (PROMIS®). The internal reliability on PROMIS® scale of anxiety had a Cronbach's alpha 0.89 (Kroenke et al., 2014). Stone et al., 2015) examined ecological validity on eight PROMIS® tests including anxiety and depression. Daily scores were taken and averaged and then compared to seven-day recall and compared to the average levels of depression or anxiety. Three types of ecological validity were examined: group differences, correspondence between the daily diaries and the 7-day recall and change over time (Stone et al., 2015). In the scores from the depression scales and the anxiety scales, all three types of ecological validity had correlations greater than 0.85.

Sleep disturbance

Sleep disturbance was measured using the PROMIS® CAT for sleep disturbance test. It assesses quality and depth of sleep and its associated restorations; perceived difficulties and concerns regarding getting to sleep or staying asleep (PROMIS®). The reliability was reported Cronbach's $\alpha = 0.96$ (Yu et al., 2011). Convergent validity of the Sleep Disturbance measure was supported with moderate to high correlations with existing scale the Pittsburgh Sleep Quality Study, and the items were reviewed by experts for content (Yu et al., 2011).

Functional Performance

Physical Function. Physical Function was measured using PROMIS® physical function CAT. This test assesses the ability and the frequency within a specified timeframe in which a person carries out self-care activities to more complex actions; the stem is "Are you able to . . ?" (HealthMeasures, 2017). The computerized adaptive test of physical function was found to be superior to static forms of equal length (Fries, Cella, Rose, Krishnan, & Bruce, 2009). PROMIS® Physical Function has been validated in persons with rheumatoid arthritis (Bartlett et al. 2015), orthopedic trauma (Stuart et al. 2015), heart failure (Flynn, 2015) and a person with cancer (Jensen et al., 2015).

Social Participation. Social participation was measured using PROMIS® ability to participate in social roles and activities scale. The participant answers regarding their ability to perform roles such as work, family responsibilities, and discretionary social activities on a 5-point Likert scale that is anchored never to always. The internal reliability is Cronbach's alpha .99. The correlation with the FACIT-Functional Well Being Scale was 0.76. (Cella et al., 2010).

Life Satisfaction

Life satisfaction was measured with the NIH Toolbox® General Life Satisfaction Survey. It is a CAT self-report measure that assesses general feelings of one's life. The CAT consists of a Likert scale with items being five or seven item response ranging from strongly disagree to strongly agree. The internal reliability is Cronbach's $\alpha = 0.91$ (Salsman et al., 2014).

Feasibility and Acceptability

We examined feasibility and acceptability with a brief survey that was administered at the completion of the exam. There were six items on a Likert scale and two open-ended

questions. The six-items included: was adequate instruction given to complete the required tasks, the screen was easy to read, the use of the keyboard was easy, whether there was a need to take a break, and a rating of the overall impression of the experience (for more information see Appendix U: Table 25 U. 1 Feasibility and Acceptability Survey).

Data Analysis

The NIH Assessment calculated and reported fully corrected T-scores based on age, gender, race/ethnicity and educational attainment for all PROMIS and NIHTB-CB tests. Statistical Analysis was performed using SPSS Version 24. Descriptive statistics were analyzed for all continuous variables. Cognitive scores of individual participants were compared to T-scores to determine the number of individuals that had a deficit of at least one standard deviation. Spearman rho Correlation coefficients were calculated for disease severity, domain-specific cognition, related factors, functional performance and life satisfaction

Results

Population Characteristics

Population characteristics are presented in Table 7 (for more information see Table 7 Sample Characteristics from the Pilot Study (n = 19)).

Feasibility and Acceptability

On a scale of 0 – 5, adequate instructions were rated 4.6, the ease of reading the tablet was 4.7, length of the test too long 3.7, agreement with not needing to take a break was 4.2, an overall impression of the experience was 4.3. In open ended declined to complete the questioning, 37% would like to see the computerized voice different, 16% said it was annoying and 21% felt it used the phrase “good job’ too frequently; 10.5% of participants felt that too many pictures were used in the Picture Sequence Memory test. As for format, 42% of

the participants suggested that the format should stay the same (for more information see Table 8 Responses to Open-ended Questions on Feasibility and Acceptability Survey (N = 19)).

Observations from a researcher's perspective, it was important to sit next to the participant to facilitate the testing as there are times both Participant and researcher need to see the screen. During the exam one participant saw the Picture Sequence Memory screen and declined to complete the test. This participant had completed the tutorial which had only four pictures. When she observed the screen with 15 pictures to be placed back in order presented, she stated that no one could remember all those pictures and she declined to attempt the task. Her data could not be included in the crystallized cognition or total cognitive score. Midway through research time frame, an error message appeared on the tablet when opening the NIHTB application. The message stated the program needed to be rebooted as there was an error in scoring. Scores were adjusted for three of the subjects that completed the pilot.

In the following cognitive tests, none of the participants showed significant deficits: executive function measured by Dimension Card Sort, language measured by Oral Reading, and crystallized and total cognition. Four domains of cognition had one person (5.3%) show significant deficit language as measured by Picture Vocabulary, working memory, fluid cognition. Two persons (11.1%) showed significant deficit in episodic memory. On the Flanker test for executive function and attention, four persons (21%) had a significant deficit. Nine persons (47.4%) had deficits in processing speed as measured by Pattern Comparison test. There were at least four persons in each domain of related factors that exhibited deficits. Four persons (21%) of the participants had significantly increased fatigue

Table 7 Sample Characteristics from the Pilot Study (n=19)

Variable	N	Percentage
Gender		
Female	12	63.2
Male	7	36.8
Education		
11th grade	2	10.5
HS	3	15.8
< 1-year college	3	15.8
1-year college	6	31.6
AD	1	5.3
BA	2	10.5
PhD	1	5.3
Smoking status		
former smokers	17	89.5
current smokers	2	10.5
Oxygen therapy	2	10.5
Exacerbations per year hospitalized in past year with exacerbation	2	10.5
GOLD COPD Stage	0	0
GOLD Stage I (mild)	9	47.4
GOLD Stage II (moderate)	6	31.6
GOLD Stage III (severe)	4	21
GOLD Stage IV (very severe)		
mMRC		
Grade 0	0	0
Grade 1	6	31.6
Grade 2	4	21.1
Grade 3	2	10.5
Grade 4	1	5.3
	Min/Max	Mean(SD)
Age	57 - 80	68.15 (7.39)
Comorbid Conditions	0 - 11	2.15 (3.14)
FEV_1	18 -71	46.4 (15.8)

Table 8 Responses to Open-Ended Questions on Feasibility and Acceptability Survey (N=19)

What would you like to see done differently?	N
"Repetitive robot voice is very annoying."	3
"quit saying 'good job"'	4
“nothing”	3
“more time”	1
"Use less words to remember, just by 2."	1
Regarding the NIH Picture Sequence Memory Test "no one can complete putting all pictures back in order” “not so many pictures”	2
What would you like to stay the same?	
"all good"	2
"good format."	3
"Like the shape and colors, the best."	1
“everything”	2
“okay”	1
“no comment”	1

and anxiety with a decrease in ability to participate in social activities. Five persons (26.3%) had a significant increase in sleep disturbance. Nine persons (47.4%) had significant increase in depressive symptoms. Nine persons (47.4%) had decrease in physical function with eleven (57.9%) decrease (for more information see Table 9: Descriptive for Domain-Specific Cognition, Functional Performance and Life Satisfaction from PROMIS and the NIHTB-CB).

Correlations between cognitive domains and related factors

The correlations between cognitive domains and related factors, there was no association between disease severity, dyspnea, or anxiety and any of the cognitive domains. There was a negative association sleep disturbance and working memory (r_s = -.512, $p < 0.05$). Correlations between functional performance and domains of cognition, were the

domain of episodic memory and social participation (r_s = - .663, p < .001) There were no significant correlations with life satisfaction (for more information see Appendix V: Table 26 V. 1 Correlations of Domain-specific Cognition, Related Factors, Functional Performance, and Life Satisfaction – Spearman Rho).

Discussion

In this pilot study, no aggregate score in any domain of cognitive function reached a level of deficit. The domain of processing speed had the greatest number of participants. The use of PROMIS® and NIHTB-CB are both feasible and acceptable to use in the persons with COPD. The overall format was acceptable to all participants. The instruments were easy to administer. The instructions provided were clear. There were no difficulties with instructions or readability of the tablet. The most frequent complaint from participants was the computerized voice saying, "great job" after every item in the practice tests.

with decline. However, all the domains of cognition had at least one individual with a deficit score of one standard deviation below the T-score. The domain of processing speed approached the level of an aggregate score deficit with a mean of 43.6 (14.6) with 47.5% (n= 9) of participants having a score that was at least one standard deviation below the T-score. The findings of this study are consistent with previous research.

Another CAT for assessing cognition, the Central Nervous System Vital Sign although the domains and tests were slightly different than the NIHTB-CB had similar findings. Over half (51.8%) of persons with COPD had (51.8%) had impaired functioning on 1 or more cognitive domains (Campman, Ranst, Meijer, & Sitskoorn, 2017). Processing speed had the greatest difference from the normative mean performance and the scores fell in the low average category indicating a slight deficit and impairment.

Table 9 Descriptive Statistics for Domain-Specific Cognition, Functional Performance and Life Satisfaction from PROMIS and the NIHTB-CB (n=19)

	Mean (SD)	Min/Max	At least 1 SD below T-Score % (N)
NIHTB-CB			
Flanker Executive Function & Attention	50.3 (8.4)	32 - 63	21 (4)
Dimension Card Sort Executive Function	57.7 (12.4)	44 - 85	0
Picture Sequence[2] Episodic Memory	51.8 (8.7)	37 - 69	11.1 (2)
Picture vocabulary Language	56.3 (9.4)	39 - 77	5.3 (1)
Oral Reading Language	64.9 (8.9)	47 - 77	0
Pattern Comparison Processing Speed	43.6 (14.6)	14 - 73	47.4 (9)
List Sort Working Memory	56.3 (9.1)	39 - 70	5.3 (1)
Fluid Cognition[2]	56.4 (9.7)	40 - 73	5.3 (1)
Crystallized Cognition[2]	62 (8.8)	52 - 79	0
Total Cognition[2]	61.5 (8.7)	49 - 77	0
Life Satisfaction	50 (8.4)	40 - 76	5.3 (1)
PROMIS® CAT Assessments			
Fatigue[1]	52.7 (7.8)	39 – 69	21 (4)
Anxiety[1]	54.8 (6.9)	44 - 67	21 (4)
Depression[1]	52.3 (8.0)	38 – 71	47.4 (9)
Sleep Disturbance[1]	48.6 (10.4)	28 – 63	26.3 (5)
Physical Function	40.9 (7.6)	28 – 53	47.3 (9)
Mobility	39.5 (6.4)	29 – 53	57.9 (11)
Participate in social activities	47.6 (9.1)	31 – 63	21 (4)

[1]One SD above population; an undesirable outcome

[2] N = 18: missing data

(Campman et al., 2017, p.3077). However, several factors need to be considered when administering a cognitive battery. First, it is common for persons in the general population to obtain one or more low scores (Holdnack et al., 2017; Mistridis et al., 2015). Second, the

more tests included in the battery, the higher the probability that an individual will have a low score on a test (Holdnack et al., 2017; Mistridis et al., 2015). In the general population, 42.7% - 45.9% would meet the criterion of the DSM-5 for mild neurocognitive disorder as defined by at least one standard deviation below the mean standard score (Holdnack et al., (2017). Thus, using a standardized battery such as the NIHTB-SB which uses seven tests to exam five domains of cognition has the potential to eliminate obtaining artificially elevated predications of cognitive decline caused by testing procedures.

When comparing cognitive scores to standardized mean scores, many characteristics of the individual must be considered. These factors include a person's level of intellectual ability, education level, physical health status, lifetime occupation and past performance of cognitive tests (Ardila, Ostrosky-Solis, Rosselli, Gomez, 2000; Apolinario et al., 2013; Bento-Torres et al., 2017; Bergman & Almkvist, 2015; Holdnack et al., 2017; Mistridis et al, 2015). Many neuropsychological tests especially those that involve language, are sensitive to educational levels (Ardila et al., 2000; Bento-Torres et al., 2017). Less education early in life is a risk factor for age-related cognitive decline, with a much stronger influence than age itself (Bento-Torres et al., 2017). In contrast, our findings did not support a difference on tests of language. Of the participants in this study, 63.2% had high school education and no more than one year of college. Two tests were given for language and between the two tests, only one participant showed deficit.

In a preliminary estimate of the strength of the relationship among domain-specific cognition, functional performance and life satisfaction in persons with mild to severe COPD, there was limited evidence to support a relationship. There only significant relationship was between social participation and episodic memory.

There is limited research on sleep disturbances in persons with COPD and domain-

specific cognition. A weak correlation was found between COPD and copying ability on the MMSE which reflects executive and visuospatial functions (Cleutjens et al., 2016). In contrast, there was no a significant relationship between sleep disturbance and executive function in our sample. There was a moderate negative correlation between sleep disturbance and working memory. The finding supports findings from previous research. In persons with COPD, memory scores were significantly worse but there was no significant difference in on three tests of executive function (Omachi et al., 2012).

Limitations of the study include that it was a pilot study with a small sample size. In examining, the correlations between cognitive domain and other variables in the model may have been limited due to the sample size and large range of scores.

In conclusion, the PROMIS® and NIHTB-CB assessments are both feasible and accessible for performing cognitive testing in the COPD patient population. Processing speed seems to be the most frequently occurring deficit. A decline in processing speed may be the first decline to occur in the pattern of decline in COPD. Sleep disturbance has a negative correlation with working memory. Further work needs to be completed to understand the complexity of pattern of domain-specific cognitive decline in persons with COPD.

BIBLIOGRAPHY

Akshoomoff, N., Newman, E., Thompson, W., Connor, M., Bloss, C., Chang, L., . . . Pediatric Imaging, N. a. G. S. (2014). The NIH Toolbox Cognition Battery: Results from a Large Normative Developmental Sample (PING). *Neuoropsychology, 28*(1), 1-10. http://dx.doi.org/10.1037/neu0000001.

Allen, S. C., Jain, M., Ragab, S., & Malik, n. (2003). Acquisition and short-term retention of inhaler techniques require intact executive functioning elderly subjects. *Age and Ageing, 32*, 299-302.

Allen, S. C., Warwick-Sanders, M., & Baxter, M. (2009). A comparison of four tests of cognition as predictors of inability to learn to use a metered dose inhaler in old age. *The International Journal of Clinical Practice, 63*(8), 1150-1153.

Ameringer, S., Elswick, R., Menzies, V., Robins, J., Starkweather, A., Walter, J., & Jallo, N. (2016). Psychometric Evaluation of the Patient-Reported Outcome Measurement Information System Fatigue-Short Form Across Diverse Populations. *Nursing Research, 65*(4), 279-289. http://dx.doi.org/10.1097/NNR.0000000000000162

Antonelli-Incalzi, R., Corsonello, A., Trojano, L., Acanfora, D., Spada, A., Izzo, O., & Rengo, F. (2008). Correlation between cognitive impairment and dependence in hypoxemic COPD. *Journal of clinical and experimental neuropsychology, 30*(2), 141-150.

Apolinario, D., Brucki, S., de Lucena Feretti, R., Farfel, J., Magaldia, R., Busse, A., & Jacob-Filho. (2013). Estimating Premorbid Cognitive Abilities in Low-Educated Populations. *PLoS ONE, 8*(8), e60084. http://dx.doi.org/10.1371/journal.pone.006084

Ardila, A., Osrosky-Solis, F., Rosselli, M., & Gomez, C. (2000). Age-Related Cognitive Decline During Normal Aging: The Complex Effect of Education. *Archives of Clinical Neuropsychology, 15*(6), 495-513.

Baltes, P. B. (1997). On the Incomplete Architecture of Human Ontogeny Selection, Optimization, and Compensation as Foundation of Developmental Theory. *American Psychologist, 52*(4), 366-380.

Bartlett, S., Orbai, A., Duncan, T., DeLeon, E., Ruffing, v., Clegg-Smith, K., & Bingham, C. I. (2015). Reliability and Validity of Selected PROMIS Measures in People with Rheumatoid Arthritis. *PLoS ONE, 10*(9), 14. http://dx.doi.org/e0138543.10.1371/journal.pone.0138543

Bento-Torres, N., Bento-Torres, J., Tomas, A., Costa, V., Crrea, P., Costa, C., . . . Picanco-Diniz, C. (2017). Influence of schooling and age on cognitive performance in healthy older adults. *Brazilian Journal of Medical and Biological Research, 50*(4), e5892. http://dx.doi.org/10.1590/141-431X20165892

Bergman, I., & Almkvist, O. (2015). Neuropsychological test norms controlled for physical health: Does it matter? *Scandinavian Journal of Psychology, 56*, 140-150. http://dx.doi.org/10.1111/sjop.12170

Bjorner, J., Rose, M., Gandek, B., Stone, A., Junghaenel, D., & Ware, J. J. (2014). Method of Administration of PROMIS Scales Did Not Significantly Impact Score Level, Reliability or Validity. *J Clin Epidemiol, 67*(1), 108-113. http://dx.doi.org/10.1016/j.jclinepi.2013.07.016.

Blinderman, C., Homel, P., Billings, A., Tennstedt, S., & Portenoy, R. (2009). Symptom Distress and Qualify of LIfe in Patients with Advanced Chronic Obstructive Pulmonary Disease. *Journal of Pain and Symptom Management, 38*(1), 115-123. http://dx.doi.org/10.1016/j.jpainsymman.2008.07.006

Campman, C., Ranst, D., Meijer, J., & Sitskoorn, M. (2017). Computerized screening for cognitive impairment in patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease, 12*, 3075-3083.

Cella, D., Riley, W., Stone, A., Rothrock, N., Reeve, B., Yount, S., . . . Hays, R. (2010). Initial Adult Health Item Banks and First Wave Testing of the Patient-Reported Outcomes Measurement Information System (PROMIS) Network: 2005-2008. *J Clin Epidemiol, 63*(11), 1179-1194. http://dx.doi.org/10.1016/j.jclinepi.2010.04.011.

Cleutjens, F. A., Spruit, M. A., Ponds, R. W., Dijkstra, J. B., Franssen, F. M., Wouters, E. F., & Janssen, D. J. (2014). Cognitive functioning in obstructive lung disease: results from the United Kingdom biobank. *J Am Med Dir Assoc, 15*(3), 214-219. http://dx.doi.org/10.1016/j.jamda.2013.12.007

Dal Ben, S., & Bricolo, F. P. (2012). The Psychological and Cognitive Profile. In R. W. Dal Negro & R. Hodder (Eds.), *Long-Term Oxygen Therapy: new insight and perspectives* Milan, Italia: Springer.

Dal Negro, R. W., Bonadiman, L., Tognella, S., Bricolo, F. P., & Turco, P. (2014). Extent and prevalence of cognitive dysfunction in chronic obstructive pulmonary disease, chronic non-obstructive bronchitis, and in asymptomatic smokers, compared to normal reference values. *Int J Chron Obstruct Pulmon Dis, 9*, 675-683. http://dx.doi.org10.2147/COPD.S63485

Dodd, J. W., Getov, S. V., & Jones, P. W. (2010). Cognitive function in COPD. *Eur Respir J, 35*, 913-922. http://dx.doi.org/10.1183/09031936.00125109

Eisner, M., Iribarren, C., Blanc, P., Yelin, E., Ackerson, L., Byl, N., . . . Katz, P. (2011). Development of disability in chronic obstructive pulmonary disease: beyond lung function. *Thorax, 66*, 108-114. http://dx.doi.org/10.1136/thx.2010.137661

Favalli, A., Miozzo, A., Cossi, S., & Marengoni, A. (2008). Differences in neuropsychological profile between healthy and COPD older persons. *Int J Geriatr Psychiatry, 23*(2), 220-221. http://dx.doi.org/10.1002/gps.1847

Feng, L., Lim, M. L., Collinson, S., & Ng, T. P. (2012). Pulmonary function and cognitive decline in an older Chinese population in Singapore. *COPD, 9*(5), 555-562. http://dx.doi.org/10.3109/15412555.2012.706341

Ferrans, C., Zerwic, J., Wilbur, J., & Larson, J. (2005). Conceptual Model of Health-Related Quality of LIfe. *Journal of Nursing Scholarship, 37*(4), 336-342.

Fioravanti, M., Nacca, D., Amati, S., Buckley, A., & Bisetti, A. (1995). Chronic Obstructive Pulmonary Disease and Associated Patterns of Memory Decline. *Dementia, 6*, 39-48.

Flynn, K., Dew, M., Lin, L., Fawzy, M., Graham, F., Hahn, E., . . . Weinfurt, K. (2015). Reliability and construct validity of PROMIS measures for patients with heart failure who undergo heart transplant. *Qual Life Res, 24*, 2591-2599. http://dx.doi.org/10.1007/s11136-015-1010-y

Fries, J., Cella, D., Rose, M., Krishnan, E., & Bruce, B. (2009). Progress in Assessing Physical Function in Arthritis: PROMIS Short Forms and Computerized Adaptive Testing. *J Rheumatol, 36*(9), 2061-2066.

Grant, I., Heaton, R., McSweeny, J., Adams, K., & Timms, R. (1982). Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease. *Arh Intern Med, 142*, 1470-1476.

Heaton, R., Akshoomoff, N., Tulsky, D., Mungas, D., Weintraub, S., Dikmen, S., . . . Gershon, R. (2014). Reliability and Validity of Composite Scores from the NIH Toolbox Cognitive Battery in Adults. *J International Neuropsychol Soc, 20*(6), 588-598. http://dx.doi.org/10.1017/S1355617714000241.

Holdnack, J., Tulsky, D., Brooks, B., Slotkin, J., & Gershon, R. (2017). Interpreting Patterns of Low Scores on the NIH Toolbox Cognition Battery. *Archives of Clinical Neuropsychology, 32*, 574-584. http://dx.doi.org/10.1093/arclin/acx032

Hung, W., Wisnivesky, J., Siu A., & Ross, J. (2009). Cognitive Decline among Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory Critical Care Medicine, 180*, 134-137. http://dx.doi.org/10.1164/rccm.200902-0276OC

Incalzi, R. A., Gemma, A., Marra, C., Capparella, O., Fuso, L., & Carbonin, P. (1997). Verbal Memory Impairment in COPD: Its Mechanisms and Clinical Relevance. *CHEST, 112*, 1506-1513.

Incalzi, R. A., Marra, C., Giordano, A., Calcagni, M., Cappa, A., Basso, S., . . . Fuso, L. (2003). Cognitive impairment in chronic obstructive pulmonary disease A neuropsychological and spect study. *J Neurol, 250,* 325-332. http://dx.doi.org/10.1007/s00415-003-1005-4

Jensen, R., Potosky, A., Reeve, B., Hahn, E., Cella, D., Fries, J., . . . Moinpour, C. (2015). Validation of the PROMIS physical function measure in a diverse US population-base cohort of cancer patients. *Qual Life Res, 24,* 2333-2344. http://dx.doi.org/10.1007/s11136-015-0992-9

Jopp, D., & Smith, J. (2006). Resources and LIfe-Management Strategies as Determinants of Successful Aging: On the Protective Effect of Selection, Optimization and Compensation. *Psychology and Aging, 21*(2), 253-265. http://dx.doi.org/10.1037/0882-7974.21.2.253

Katz, P., Gregorich, S., Eisner, M., Julian, L., Chen, H., Yelin, E., & Blanc, P. (2010). Disability in Valued LIfe Activities among Individuals with COPD ad Other Respiratory Conditions. *J Cardiopulm Rehabil Prev, 30*(2), 126-136. http://dx.doi.org/10.1097/HCR.0b013e3181be7e59

Kronenke, K., Yu, Z., Wu, J., Kenet, T., & Monahan, P. (2014). Operating Characteristics of PROMIS Four-Item Depression and Anxiety Scales in Primary Care Patients with Chronic Pain. *Pain Medicine, 15,* 1892-1901.

Leidy, N. (1994). Functional status and the forward progress of merry-go-rounds: toward a coherent analytical framework. *Nur Res, 43*(4), 196-202.

Levy, B., Slade, M., & Kasl, S. (2002). Longitudinal Benefit of Positive Self-Perceptions of Aging on Functional Health. *Psychological Science, 57B*(5), 409-417.

Mahler, D., Ward, J., Waterman, L., McCusker, C., ZuWallack, R., & Baird, J. (2009). Patient-Reported Dyspnea in COPD Reliability and Association with Stage of Disease. *CHEST, 136,* 1473-1479. http://dx.doi.org/10.1378/chest.09-0934

Martinez, C., Richardson, C., Han, M., & Cigolle, C. (2014). Chronic Obstructive Pulmonary Disease, Cognitive Impairment and Development of Disability: The Health Retirement Study. *AnnalsATS, 11*(9), 1362-1370. http://dx.doi.org/10.1513/AnnalsATS.20145-187OC

Mistridis, P., Egli, S., Iverson, G., Berres, M., Willmes, K., Welsh-Bohmer, K., & Monsch, A. (2015). Considering the base rates of low performance in cognitively healthy older adults improves accuracy to identify neurocognitive impairment with the Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Assessment Battery (CERAD_NAB). *Eur Arch Psychiartry Clin Neurosci, 265,* 407-417. http://dx.doi.org/10.10007/s00406-014-0571-z

Omachi, T., Blanc, P., Claman, D., Chen, H., Yelin, E., Julian, L., & Katz, P. (2012). Disturbed Sleep among COPD Patients is Longitudinally Associated with Mortality and Advers COPD Outcomes *Sleep Medicine, 13*(5), 476-483. http://dx.doi.org/10.1016/j.sleep.2011.12.007

Ozge, C., Ozge, A., & Unal, O. (2006). Cognitive and functional deterioration in patients with severe COPD. *Behavioural Neurology, 17*, 121-130.

Salsman, J., Lai, J., Hendrie, H., Butt, A., Zill, N., Pilkonis, P., . . . Cella, D. (2014). Assessing Psychological Well-Being: Self-Report Instruments for the NIH Toolbox. *Qual Life Res, 23*(1), 205-215. http://dx.doi.org/10.1007/s11136-013-0452-3.

Schillerstrom, J., Horton, M., & Royall, D. (2005). The Impact of Medical Illness of Executive Function. *Psychosomatics, 46*, 508-516.

Senders, A., Hanes, D., Bourdette, D., Whitham, R., & Shinto, L. (2015). Reducing survey burden: Feasibility and validity of PROMIS measures in multiple sclerosis. *Mult Scler, 20*(8), 1102-1111. http://dx.doi.org/10.1177/1352458513517279

Singh, B., Mielke, M., Parsaik, A., Cha, R., Roberts, R., Scanion, P., . . . Peterson, R. (2014). A Prospective Study of Chronic Obstructive Pulmonary Disease and the Risk for Mild Cognitive Impairment. *JAMA Neurol, 71*(5), 581-588. http://dx.doi.org./10.001/jamaneurol.2014.94

Stone, A., Broderick, J., Junghaenel, D., Schneider, S., & Schwartz, J. (2015). PROMIS Fatigue, Pain Intensity, Pain Interference, Pain Behavior, Physical Function, Depression, Anxiety, and Anger Scales Demonstrate Ecological Validity. *Journal of Clinical Epidemiology*. http://dx.doi.org/10.1016/j.jclinepi.2015.08.029

Stuart, A., Higgins, T., Hung, M., Weir, C., Kubiak, E., Rothberg, D., & Saltzman, C. (2015). Reliability in Measuring Preinjury Physical Function in Orthopaedic Trauma. *J Orthop Trauma, 29*(12), 527-532.

Thakur, N., Blanc,P., Julian L., Yelin, E., Katz, P, Sidney, S., Iribarren, C., & Eisner, M. (2010). COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. *International Journal of Chronic Obstructive Pulmonary Disease, 5*, 263-269.

Torres-Sanchez, I., Rodriquiez-Alzueta, E., Cabrera-Martos, I., Lopez-Torres, I., Moreno-Ramirez, M., & Valenze, M. (2015). Cognitive Impairment in COPD: a systematic review. *J Bras Pneumol, 41*(2), 182-190. http://dx.doi.org/10.1590/S1806-37132015000004424

Weintraub, S., Dikmen, S., Heaton, R., Tulsky, D., Zelzso, D., Slotkin, J., . . . Gershon, R. (2014). The Cognitive Battery of the NIH Toolbox for Assessment of Neurological and Behavioral Function: Validation in an Adult Sample. *Journal international Neuorphyshol Soc, 20*(6), 567-578. http://dx.doi.org/10.1017/S1355617714000320

Yanker, B., Lu, T., & Loerch, P. (2008). The Aging Brain. *Annu Rev Pathol Mech Dis, 3*, 41-46. http://dx.doi.org/10.1146/annurev.pathmechdis.2.010506.092044

Yu, L., Buysse, D., Germain, A., Moul, D., Stover, A., Dodds, N., . . . Pilkonis, P. (2011). Development of Short Forms from the PROMIS Sleep Disturbance and Sleep-Related Impairment Item Banks. *Behav Sleep Med, 10*(1), 6-24. http://dx.doi.org/10.1080/15402002.2012.636266.

CHAPTER V

Discussion

In persons with COPD, the relationship among domain-specific cognition, functional performance and life satisfaction is not fully understood. From the systematic review, there is strong evidence of decline in domain-specific cognition. Comparisons across studies are complicated by no universal categorization of the domains of cognition and a vast array of measurements used to assess each domain. In prior reviews, domains were discussed by those most frequently assessed. We expanded the knowledge in relationship to domain-specific cognitive decline by performing a meta-analysis. Persons with COPD had poorer performance in all domains of cognition. A large effect size in the domains of executive function and processing speed were found with processing speed having the largest effect size.

COPD has been related to structural brain changes. A plausible reason for the significant decline in executive function and processing speed in persons with COPD can be related to these structural changes. The white matter of the frontal cortex is involved in executive function, short-term recall and processing speed (Yankner, Lu, & Loerch, 2008). These frontal circuits which are associated is particularly sensitive to hypoperfusion and hypoxia (Schilerstrom, Horton, & Royall, 2005). Substantial perfusion deficits were found in the frontal lobes of persons with COPD and were most marked in oxygen users (Incalzi, 2003). Also, from chronic inflammation there are elevated levels of choline which leads to changes in white matter (Borson, 2008). These structural changes that occur in COPD lead to deficits in cognitive functioning.

From the HRS data base, persons with COPD, at time of first reported diagnosis of COPD, were found to have a significant decrease in the domains of executive function and memory and learning. The difference held true over the 12-year period apart from immediate recall at which time there was no longer a difference between the two groups. The slope of change did not differ significantly except for immediate recall. The slope of immediate recall was steeper in the non-COPD group. The decline was such that after 12 years, the mean differences between the two groups were no longer significant. However, the non- COPD group continued to have better performance than those with COPD.

There are three differences to be explained; the difference at baseline between the mean scores of the group the similar slopes of decline in executive function and delayed recall and the steeper slope in immediate recall in the non-COPD group. The difference at baseline could be caused by COPD leading to cognitive changes earlier in life. A few studies have suggested that cognitive changes may occur prior to the diagnosis of COPD (Dal Ben and Bricolo, 2012; Dal Negro et al., 2014) . One reason that there may not be a difference in the slope of change between groups is that 85% of the person in the HRS data had quit smoking. Thus, with the cessation of smoking, the rate of decline in lung function slows which may subsequently lead to a decline in the consequences of damaged lung function such as cognitive decline. In contrast, in the non-COPD group one domain of cognition had a steeper slope, immediate recall. This may in part be explained by critical ages in the life course of the brain. One critical age is between the ages of 60-90, when brain volume shrinkage occurs with the steepest estimated decline in cerebral white matter and hippocampus (Fjell et al., 2013). These areas of the brain are involved in executive function, immediate recall and processing speed.

Attempting to understand the relationship between domain-specific cognition, functional performance and life satisfaction, we examined the potential that the relationship between cognitive decline and life satisfaction was mediated by functional performance. In all areas of functional performance; mobility, use of large muscles, gross motor and fine motor skills, persons with COPD preformed significantly worse than the non-COPD group. However, a mediation effect could not be established as there was no significant relationship between any of the domains of cognition and life satisfaction in the COPD group. In the non-COPD group, delayed recall had a significant relationship with life satisfaction and it was fully mediated by functional performance.

The lack of a significant relationship between domain-specific cognition and life satisfaction could be a result that life satisfaction remains relatively stable over time. The focus of this research was on cognition; thus, life satisfaction was only examined in the cross-sectional analysis in a time when many persons already had been diagnosed with COPD for several years. Prior to our analysis, the person with COPD could have used a life management strategy such as selection, optimization and compensation(SOC) (Baltes, 1997). SOC is an active process by which one chooses and prioritizes goals and tasks, invests resources needed and finally compensates using external means to achieve goals (Jopp & Smith, 2006). Optimal use of resources through strategies such as SOC may prevent feelings of dissatisfaction (p.262). Additionally, we examined functional performance from the activities that are required to perform ADLs and IADLs. However, examining function from the perspective of valued life activities may be helpful in the future, as valued life activities are more strongly linked to quality of life than ADLs and IADLs (Katz et al., 2010).

Other factors were identified as having the potential to impact cognitive domains. From the psychosocial variables available in the HRS data, we focused on need for cognition, the sense of mastery, hopelessness and satisfaction with aging. The sense of mastery was not a significant predicator of cognition in either group. The need for cognition and satisfaction with aging were weak predictors of cognition in the non-COPD group only. However, hopelessness was a predictor of cognition in both groups but was a stronger predictor in the COPD group in immediate and delayed recall. In fact, of the variable examined, it was the strongest predicator.

It becomes apparent just as we cannot isolate and study just one domain of cognition, it is equally difficult to separate emotions from the study of cognition. One such emotion is our negative or positive perception of self. As people experience life, they develop attitudes and predication about aging from information in society and experiences with older person (Levy, Slade, & Kasl, 2002). When these attitudes are internalized they become part of one's self-perception of aging. With aging, these self-perceptions can become self-fulfilling prophecies. It was found that given the same functional health at baseline, over a span of 20 years, persons with a negative self-perception of aging had a greater functional decline that was partially moderator by self-control (pP414). Hopelessness may have a strong influence on cognition in persons with COPD as they are aware that their disease is manageable but not curable and a weaker predictor in the non-COPD group aging occurs out of one's control. Hopelessness was just examined in the cross-sectional portion of the study. A future direction would be to examine it in relationship between baseline hopelessness and cognition, functional performance and life satisfaction over time.

The last part of the study was to examine the feasibility and acceptability of using CAT to test cognition in persons with COPD. The format was well received by all participants. It is a

very feasible and acceptable format for using in the COPD population. We examined aggregate data to assess for declines in any of the cognitive domains. In the aggregate data, no domain was shown to have a significant level of decline. However, there was at least one person in every domain that reached the level of having a deficit. The domain of processing speed showed the largest number of persons with deficit, 47.5% of participants which is consistent with other findings.

The NIHTB-CB was used for this pilot study. However, there are other CATs for testing cognition available. As there in no universal categories for domain-specific cognition, there remains incontinences in labeling domains and tests included. The movement towards standardize testing will be helpful in cognitive assessment. But there remains the lack of universal categorization of domains of cognition and the best tests for each domain. The use of the tablet may be a better format than computer-based testing. However, this was not examined in this research.

From the pilot study, the relationship between domain-specific cognition, functional performance and life satisfaction, correlations of the variables were examined. There was no correlation between any of the domains of cognition and life satisfaction. In functional performance, there was a moderate negative correlation between the ability to participate in social roles and episodic memory. Related factors including disease severity, symptoms or dyspnea and fatigue and emotional states of depression and anxiety and sleep were examined for a relationship with domain-specific cognition. Only sleep disturbance had a significant negative correlation with working memory. Sleep disturbances in COPD have been well documented. Sleep was found to be correlated to memory (Omachi et al., 2012).

In summary, future directions of research include systematic review of executive function including clinical relevance. Repeating the longitudinal study including asymptomatic smokers or trace the persons COPD and include the years prior to self-reporting diagnosis of COPD. Since we could not establish a significant relationship between domains of cognition, functional performance and life satisfaction, a future direction would be to examine functional performance from a valued life activity or social performance perspective. An important future direction of research needs to be to determine clinical significance of the cognitive declines.

BIBLIOGRAPHY

Akshoomoff, N., Beaumont, J., Bauer, P., Dikmen, S., Gershon, R., Mungas, D. . . .Heaton, R. (2008). NIH Toolbox Cognitive Function Battery (CFB): Composite Scores of Crystallized, Fluid, and Overall Cognition. *Monogr Soc Res Child Dev.78*(4). 119-132. http://dx.doi.org/10.111/mono.12038

Ameringer, S., Elswick, R., Menzies, V., Robins, J., Starkweather, A., Walter, J., & Jallo, N. (2016). Psychometric Evaluation of the Patient-Reported Outcome Measurement Information System Fatigue-Short Form Across Diverse Populations. *Nursing Research, 65*(4), 279-289. http://dx.doi.org/10.1097/NNR.0000000000000162

Antonelli-Incalzi, R., Corsonello, A., Trojano, L., Acanfora, D., Spada, A., Izzo, O., & Rengo, F. (2008). Correlation between cognitive impairment and dependence in hypoxemic COPD. *Journal of clinical and experimental neuropsychology, 30*(2), 141-150.

Apolinario, D., Brucki, S., de Lucena Feretti, R., Farfel, J., Magaldia, R., Busse, A., & Jacob-Filho. (2013). Estimating Premorbid Cognitive Abilities in Low-Educated Populations. *PLoS ONE, 8*(8), e60084. http://dx.doi.org/10.1371/journal.pone.006084

Ardila, A., Osrosky-Solis, F., Rosselli, M., & Gomez, C. (2000). Age-Related Cognitive Decline During Normal Aging: The Complex Effect of Education. *Archives of Clinical Neuropsychology, 15*(6), 495-513.

Bartlett, S., Orbai, A., Duncan, T., DeLeon, E., Ruffing, v., Clegg-Smith, K., & Bingham, C. I. (2015). Reliability and Validity of Selected PROMIS Measures in People with Rheumatoid Arthritis. *PLoS ONE, 10*(9), 14. http://dx.doi.org/e0138543.10.1371/journal.pone.0138543

Campman, C., Ranst, D., Meijer, J., & Sitskoorn, M. (2017). Computerized screening for cognitive impairment in patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease, 12*, 3075-3083.

Cella, D., Riley, W., Stone, A., Rothrock, N., Reeve, B., Yount, S., . . . Hays, R. (2010). Initial Adult Health Item Banks and First Wave Testing of the Patient-Reported Outcomes Measurement Information System (PROMIS) Network: 2005-2008. *J Clin Epidemiol, 63*(11), 1179-1194. http://dx.doi.org/10.1016/j.jclinepi.2010.04.011

Dodd, J. W., Getov, S. V., & Jones, P. W. (2010). Cognitive function in COPD. *Eur Respir J, 35*, 913- 922. http://dx.doi.org/10.1183/09031936.00125109

Eisner, M., Iribarren, C., Blanc, P., Yelin, E., Ackerson, L., Byl, N., . . . Katz, P. (2011). Development of disability in chronic obstructive pulmonary disease: beyond lung function. . *Thorax, 66*, 108-114. http://dx.doi.org/10.1136/thx.2010.137661

Feng, L., Lim, M. L., Collinson, S., & Ng, T. P. (2012). Pulmonary function and cognitive decline in an older Chinese population in Singapore. *COPD, 9*(5), 555-562. http://dx.doi.org10.3109/15412555.2012.706341

Ferrans, C., Zerwic, J., Wilbur, J., & Larson, J. (2005). Conceptual Model of Health-Related Quality of LIfe. *Journal of Nursing Scholarship, 37*(4), 336-342.

Flynn, K., Dew, M., Lin, L., Fawzy, M., Graham, F., Hahn, E., . . . Weinfurt, K. (2015). Reliability and construct validity of PROMIS measures for patients with heart failure who undergo heart transplant. *Qual Life Res, 24*, 2591-2599. http://dx.doi.org/10.1007/s11136-015-1010-y

Fries, J., Cella, D., Rose, M., Krishnan, E., & Bruce, B. (2009). Progress in Assessing Physical Function in Arthritis: PROMIS Short Forms and Computerized Adaptive Testing. *J Rheumatol, 36*(9), 2061-2066.

Holdnack, J., Tulsky, D., Brooks, B., Slotkin, J., & Gershon, R. (2017). Interpreting Patterns of Low Scores on the NIH Toolbox Cognition Battery. *Archives of Clinical Neuropsychology, 32*, 574-584. http://dx.doi.org/10.1093/arclin/acx032

Hung, W., Wisnivesky, J., Siu A., & Ross, J. (2009). Cognitive Decline among Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory Critical Care Medicine, 180*, 134-137. http://dx.doi.org10.1164/rccm.200902-0276OC

Jensen, R., Potosky, A., Reeve, B., Hahn, E., Cella, D., Fries, J., . . . Moinpour, C. (2015). Validation of the PROMIS physical function measure in a diverse US population-base cohort of cancer patients. *Qual Life Res, 24*, 2333-2344. http://dx.doi.org/10.1007/s11136-015-0992-9

Kroenke, K., Yu, Z., Wu, J., Kean, J., & Monahan, P. (2014). Operating Characteristic of PROMIS Four- Item Depression and Anxiety Scales in Primary Care Patients with Chronic Pain. . *Pain Medicine, 15*, 1892-1901.

Leidy, N. (1994). Functional status and the forward progress of merry-go-rounds: toward a coherent analytical framework. *Nur Res, 43*(4), 196-202.

Mahler, D., Ward, J., Waterman, L., McCusker, C., ZuWallack, R., & Baird, J. (2009). Patient-Reported Dyspnea in COPD Reliability and Association with Stage of Disease. *CHEST, 136*, 1473-1479. http://dx.doi.org/10.1378/chest.09-0934

Martinez, C., Richardson, C., Han, M., & Cigolle, C. (2014). Chronic Obstructive Pulmonary Disease, Cognitive Impairment and Development of Disability: The Health Retirement Study. *AnnalsATS, 11*(9), 1362-1370. http://dx.doi.org/10.1513/AnnalsATS.20145-187OC

Mistridis, P., Egli, S., Iverson, G., Berres, M., Willmes, K., Welsh-Bohmer, K., & Monsch, A. (2015). Considering the base rates of low performance in cognitively healthy older adults improves accuracy to identify neurocognitive impairment with the Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Assessment Battery (CERAD_NAB). *Eur Arch Psychiartry Clin Neurosci, 265*, 407-417. http://dx.doi.org/10.10007/s00406-014-0571-z

Mungas, D., Heaton, R., Tulsky, D., Zelaso, P., Slotkin, J., Blitz, D., . . . Gershon, R. (2014). Factor Structure, Convergent Validity, and Discriminant Validity of the NIH Toolbox Cognitive Health Battery (NIHTB-CHB) in Adults. *J International Neuropsychol Soc, 20*(6), 579- 587.http://dx;doi.org/10.1017/S1355617714000307

Ozge, C., Ozge, A., & Unal, O. (2006). Cognitive and functional deterioration in patients with severe COPD. *Behavioural Neurology, 17*, 121-130.

Singh, B., Mielke, M., Parsaik, A., Cha, R., Roberts, R., Scanion, P., . . . Peterson, R. (2014). A Prospective Study of Chronic Obstructive Pulmonary Disease and the Risk for Mild Cognitive Impairment. *JAMA Neurol, 71*(5), 581-588. http://dx.doi.org./10.001/jamaneurol.2014.94

Stone, A., Broderick, J., Junghaenel, D., Schneider, S., & Schwartz, J. (2015). PROMIS Fatigue, Pain Intensity, Pain Interference, Pain Behavior, Physical Function, Depression, Anxiety, and Anger Scales Demonstrate Ecological Validity. *Journal of Clinical Epidemiology*. http://dx.doi.org/10.1016/j.jclinepi.2015.08.029

Stuart, A., Higgins, T., Hung, M., Weir, C., Kubiak, E., & Rothberg, D. S., C. (2015). Reliability in Measuring Preinjury Physical Function in Orthopaedic Trauma. *J Ortho Trauma, 29*(12), 527- 532.

Thakur, N., Blanc,P., Julian L., Yelin, E., Katz, P, Sidney, S., Iribarren, C., & Eisner, M. (2010). COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. *International Journal of Chronic Obstructive Pulmonary Disease, 5*, 263-269.

Torres-Sanchez, I., Rodriquiez-Alzueta, E., Cabrera-Martos, I., Lopez-Torres, I., Moreno-Ramirez, M., & Valenze, M. (2015). Cognitive Impairment in COPD: a systematic review. *J Bras Pneumol, 41*(2), 182-190. http://dx.doi.org/10.1590/S1806-37132015000004424

Weintraub, S., Dikmen, S., Heaton, R., Tulsky, D., Zelzso, D., Slotkin, J., . . . Gershon, R. (2014). The Cognitive Battery of the NIH Toolbox for Assessment of Neurological and Behavioral Function: Validation in an Adult Sample. *Journal international Neuorphyshol Soc, 20*(6), 567-578. http://dx.doi.org/10.1017/S1355617714000320.

Yu, L., Buysse, D., Germain, A., Moul, D., Stover, A., Dodds, N., . . . Pilkonis, P. (2011). Development of Short Forms from the PROMIS Sleep Disturbance and Sleep-Related Impairment Item Banks. *Behav Sleep Med, 10*(1), 6-24. http://dx.doi.org/10.1080/15402002.2012.636266.

Zhu, B., Giovani, G., Mowery, P., & Eriksen, M. (1996). *The Relationship between Cigarette Smoking and Education Revisited: Implications for Categorizing Persons' Educational Status.* American Journal of Public Health. *86*(11). 1582-1589.

APPENDIX A

Revised Wilson and Cleary Model for Health-Related Quality of Life

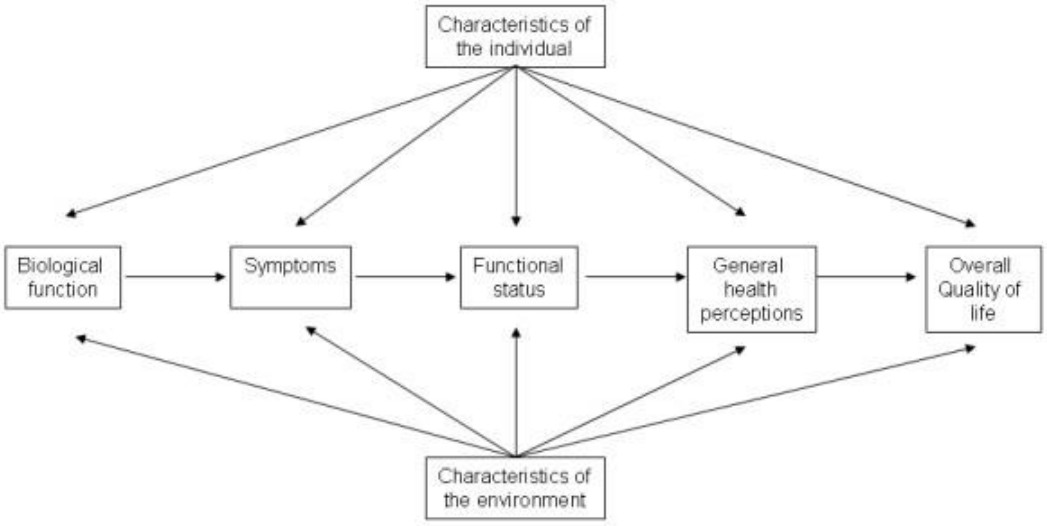


Figure 19 A. 1 Revised Wilson & Cleary Model for Health-Related Quality of Life

Retrieved from Google Images:
https://www.researchgate.net/figure/5685471_fig1_Revised-Wilson- and-Cleary-Model-for-Health-Related-Quality-Life-Revised-Wilson-and

APPENDIX B

GOLD COPD Staging System

Table 10 B. 1 GOLD COPD Staging System

Stage I	Mild COPD	$FEV_1/FVC<0.70$	$FEV_1 \geq 80\%$ normal
Stage II	Moderate COPD	$FEV_1/FVC<0.70$	FEV_1 50-79% normal
Stage III	Severe COPD	$FEV_1/FVC<0.70$	FEV_1 30-49% normal
Stage IV	Very Severe COPD	$FEV_1/FVC<0.70$	FEV_1 <30% normal, or <50% normal with chronic respiratory failure present*

*Based on post-bronchodilator FEV_1

Global Strategy for the Diagnosis, Management, and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015.

APPENDIX C

COPD Assessment Test

Your name:

Today's date:

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

Last Updated: February 24, 2012

(COPD Assessment Test)

APPENDIX D

Modified Medical Research Center Dyspnea Scale (mMRC)

Date _____

Instructions: Choose the one best response.

Please choose the one best response to describe your shortness of breath. Grade 0 "I only get short of breath with strenuous exercise."

Grade 1 "I get short of breath when hurrying on the level or walking up a slight hill."

Grade 2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the Level"

Grade 3 "I stop for breath after walking 100 yards or after a few minutes on the level."

Grade 4 "I am too breathless to leave the house" or I am breathless while dressing."

(Modified Medical Research Council Dyspnea Scale)

APPENDIX E

Combined Assessment Tool of COPD

Table 11 E. 1 Combined Assessment Tool of COPD

Patient	Characteristic	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	< 10	0-1
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 10	≥ 2
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015.

APPENDIX F

Search Terms

1. Chronic Obstructive Airway Disease (COAD)
2. Chronic Obstructive Pulmonary Disease (COPD)
3. Chronic Bronchitis
4. Emphysema
5. 1 or 2 or 3 or 4
6. Cognition 7. 6 & 7
8. Cognitive function
9. 6 & 9
10. Executive function
11. 6 & 11
12. Perception
13. 6 & 13
14. Attention
15. 6 & 15
16. Memory
17. 6 & 17
18. Working memory
19. 6 & 19
20. “visual memory”
21. 6 & 21
22. “verbal memory”
23. 6 & 23
24. “reaction time”
25. 6 & 25
26. “processing speed”
27. 6 & 27
28. Language
29. 6 & 29
30. Visuospatial
31. 6 & 31
32. “cognitive dysfunction”
33. 6 & 33
34. “cognitive deficit”
35. 6 & 35
36. “cognitive domains”
37. 6 & 38

APPENDIX G

Study Selection Tool

Table 12 G. 1 Study Selection Tool

Criteria for Systematic Review	Yes*	No	Comments
Research Design – Descriptive Experimental Quasi-Experimental			**EXCLUDE CASE STUDIES AND QUALITATIVE STUDIES**
Participants Major focus of article COPD/chronic bronchitis patients with any of the following measures FEV1 or FEV1/FVC Blood gases Diffusion capacity PFT Lung Volume Self- Report			
Cognition Perception _____ Attention _____ Learning and Memory (declarative and/or non-declarative memory) Immediate memory _____ Delayed Memory _____ Episodic Memory _____ Working Memory _____ Long-term/ short-term memory _____ Executive Function _____ Language _____ Speed and Processing _____			****MUST HAVE AT LEAST ONE DOMAIN TO BE INCLUDED**
The following section is information: A yes is not necessary for inclusion in the review			
OUTCOME **Does the article have an outcome(s) measure?**			If yes, list outcome(s).

*All criteria boxes must be marked yes for inclusion

APPENDIX H

Data Extraction Tool

Table 13 H. 1 Data Extraction Tool

1. **Date form completed**	
2. **Name/ID of person extracting data**	
3. **Report title**	
4. **Report ID**	
5. **Reference details**	
6. **Report author contact details**	
7. **Publication type**	
8. **Study funding source**	
Possible conflicts of interest *(for study authors)*	
9. **Notes:**	

Eligibility

Study Characteristics	**Review Inclusion Criteria**	**Yes/No Unclear**	**Location in text**
10. **Type of study**	descriptive	...	
	Experimental	...	
	Quasi-experimental	...	
	Longitudinal	...	
	Observational	...	
	Cross-sectional	...	
	Case-control	...	

Study Characteristics	Review Inclusion Criteria	Yes/No Unclear	Location in text
11. **Participants** COPD & Control or age referent normal		...	
12. **Domain-specific Cognition**		...	
13. **Types of outcome measures**		...	
14. **Decision:**	...		
15. **Reason for exclusion**			
16. **Notes:**			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Population and setting

	Description	Location in text
17. **Population description**		
18. **Setting**		
19. **Inclusion criteria**		
20. **Exclusion criteria**		
21. **Method/s of recruitment of participants**		
22. **Notes:**		

Methods

	Descriptions as stated in report/paper	Location in text
23. **Aim of study**		
24. **Design**		
25. **Unit of allocation** *(by individuals, cluster/ groups or body parts)*		
26. **Start date**		
27. **End date**		
28. **Duration of participation** *(from recruitment to last follow-up)*		
29. **Notes:**		

Risk of Bias assessment

Domain	Risk of bias Low/ High/Unclear	Support for judgement	Location in text
30. **Random sequence generation** *(selection bias)*	...		
31. **Allocation concealment** *(selection bias)*	...		
32. **Blinding of participants and personnel** *(performance bias)*	...	**Outcome group: All/**	
33. **Blinding of outcome assessment** *(detection bias)*	...	**Outcome group: All/**	
34. **Incomplete outcome data** *(attrition bias)*	...		
35. **Selective outcome reporting?** *(reporting bias)*	...		
36. **Other bias**	...		
37. **Notes:**			

Participants

	Description as stated in report/paper	Location in text
38. **Total no. randomised** *(or total pop. at start of study for NRCTs)*		

	Description as stated in report/paper	Location in text
39. **Clusters** *(if applicable, no., type, no. people per cluster)*		
40. **Baseline imbalances**		
41. **Withdrawals and exclusions**		
42. **Age**		
43. **Sex**		
44. **Race/Ethnicity**		
45. **Severity of illness**		
46. **Co-morbidities**		
47. **Other treatment received**		
48. **Other relevant sociodemographic**		
49. **Subgroups measured**		
50. **Subgroups reported**		
51. **Notes:**		

Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required. For randomized or non-randomized trial - Dichotomous outcome

	Description as stated in report/paper	Location in text
52. **Comparison**		
53. **Outcome**		
54. **Subgroup**		

<table>
<tr><th></th><th colspan="4">Description as stated in report/paper</th><th>Location in text</th></tr>
<tr><td>55. Time point</td><td colspan="4"></td><td></td></tr>
<tr><td rowspan="3">56. Results

Note whether:

... post-intervention OR

... change from baseline

And whether

... Adjusted OR

...Unadjusted</td><td colspan="2">Intervention</td><td colspan="2">Comparison</td><td rowspan="3"></td></tr>
<tr><td>No. events</td><td>No. participants</td><td>No. events</td><td>No. participants</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">57. Baseline data</td><td colspan="2">Intervention</td><td colspan="2">Comparison</td><td rowspan="3"></td></tr>
<tr><td>No. event</td><td>No. part.</td><td>No. event</td><td>No. part.</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>58. No. missing participants and reasons</td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>59. No. participants moved from other group and reasons</td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>60. Any other results reported</td><td colspan="4"></td><td></td></tr>
<tr><td>61. Unit of analysis</td><td colspan="4"></td><td></td></tr>
</table>

	Description as stated in report/paper		Location in text
62. **Statistical methods used and appropriateness of these methods** *(e.g. adjustment for correlation)*			
63. **Reanalysis required?** *(if yes, specify why, e.g. correlation adjustment)*	... *Yes/No/Unclear*		
64. **Reanalysis possible?**	... *Yes/No/Unclear*		
65. **Reanalyzed results**			
66. **No test:**			

Other information

	Description as stated in report/paper	Location in text
67. **Key conclusions of study authors**		
68. **References to other relevant studies**		
69. **Correspondence required for further study information** *(what and from whom)*		
70. **Further study information requested**		

(from whom, what and when)	
71. **Correspondence received** *(from whom, what and when)*	
72. **Notes:**	

Effective Practice and Organization of Care (EPOC). *(2013)*

APPENDIX I

Sign Checklist

S I G N	**Methodology Checklist 4: Case-control studies**		
Study identification (*Include author, title, year of publication, journal title, pages*)			
Guideline topic:		Key Question No:	Reviewer:
Before completing this checklist, consider: 1. Is the paper really a case-control study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. 2. Is the paper relevant to key question? Analyze using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.			
Reason for rejection: Reason for rejection: 1. Paper not relevant to key question □ 2. Other reason □ (please specify):			
Section 1: Internal validity			
In a well conducted case control study:			*Does this study, do it?*
1.1	The study addresses an appropriate and clearly focused question.		Yes ⭘ No ⭘ Can't say ⭘
SELECTION OF SUBJECTS			
1.2	The cases and controls are taken from comparable populations.		Yes ⭘ No ⭘ Can't say ⭘

1.3	The same exclusion criteria are used for both cases and controls.	Yes ⭘ No ⭘ Can't say ⭘
1.4	What percentage of each group (cases and controls) participated in the study?	Cases: Controls:
1.5	Comparison is made between participants and non-participants to establish their similarities or differences.[i]	Yes ⭘ No ⭘ Can't say ⭘
1.6	Cases are clearly defined and differentiated from controls.	Yes ⭘ No ⭘ Can't say ⭘
1.7	It is clearly established that controls are non-cases.	Yes ⭘ No ⭘ Can't say ⭘
ASSESSMENT		
1.8	Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment.	Yes ⭘ No ⭘ Can't say ⭘ Does not apply ⭘
1.9	Exposure status is measured in a standard, valid and reliable way.	Yes ⭘ No ⭘ Can't say ⭘
CONFOUNDING		

1.10	The main potential confounders are identified and considered in the design and analysis.[ii]	Yes ⭘ No ⭘ Can't say ⭘
STATISTICAL ANALYSIS		
1.11	Confidence intervals are provided.	Yes ⭘ No ⭘
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimize the risk of bias or confounding?	High quality (++) □ Acceptable (+) □ Unacceptable – reject 0 □
2.2	Considering clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ⭘ No ⭘ Can't say ⭘
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes ⭘ No ⭘
2.4	**Notes.** Summarize the author's conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

APPENDIX J

Perception Studies

Table 14 J. 1 Perception Studies

Study	Sample	Mean Age (SD)	Mean (SD)	Sign.
Perceptual Score				
†Prigatano et al. (1983)	100 COPD 25 Controls	61.5 (7.4) 59.6 (9)	5.7(7.4) 6.0 (6.6	NS
Speech-Sound Perception Test				
†Grant et al., (1982)	51 COPD 51 Controls	64.4 (8.1) 64.3 (10.5)	11.2(n.r.) 8 (n.r.)	p < .05
†Prigatano et al. (1983)	100 COPD 25 Controls	61.5 (7.4) 59.6 (9)	7.9 (6.9) 5.9 (5.4)	NS
Sensory Exam				
†Grant et al., (1982)	51 COPD 51 Controls	64.4 (8.1) 64.3 (10.5)	12.3(n.r.) 6.4 (n.r.)	p < .001

(n.r.) = not reported

APPENDIX K

Attention Studies

Table 15 K. 1 Attention Studies

Study	Sample	Mean Age (SD)	Mean (SD)	Sign.
Bourbon-Test Measures sustained selective attention by measuring simple reaction time-consists of 33 lines with different dot patterns and patterns of 4 must be selected-scores are based on the mean time in seconds it takes to complete each line. Higher score indicates poorer cognitive performance				
†Vos et al (1995)	39 COPD 38 Control	65.9 (5) 64.8 (5)	Time in sec (SD) Overall mean line COPD: 14.1 (3) Control: 12.6 (2) Mean line time on lines 0-11 COPD: 14.4 (3) Control: 12.7 (2) Mean line time on lines11-22 COPD: 13.9 (3) Control: 12.4 (2) Mean line time on lines 22-33 COPD: 14 (3) Control: 12.7 (2)	 p< 0.05 p< 0.05 p< 0.05 p< 0.05
STROOP Measures selective attention when the name of the color is printed in a color not denoted by the name, the naming process takes extra processing time test is scored in seconds above predicted test duration based on gender and education level higher score indicates poorer cognitive performance				
†Liesker et al. (2004)	30 COPD 20 Control	64.8 (8.2) 65.6 (11.2)	Stroop Word Card COPD: 6 (-17-40.5) ** Control: 2.5 (-6-16.5) ** Stroop Color Card COPD: 3 (-18-31) ** Control: -2 (-12-36) ** Stroop Color Word Card COPD: 28 (-6-164) ** Control: 21 (-19-68) **	 NS NS NS

†Pereira, et al. (2011)	34 COPD 18 Control	65.2 (7) 62.7 (4)	*Test 1 COPD: 22 (12-38) ** Control: 19 (12-32) ** *Test 2 COPD: 28 (6.4) Control: 25.2 (7.2) *type of Stroop not specified by authors	 NS NS
Trailmaking Test A Consists of numbers 1-25 placed in circles distributed randomly over a sheet of paper -using a pencil, the numbers within the circles are connected in ascending order -the tested is scored by then number of seconds it takes to complete the test -the test is normative data based on age and education				
†Bratek et al. (2013)	12 COPD 13 Control	67(n.r.) 48(n.r.)	42.8 (n.r) 30.04 (n.r.)	Not report ed
(Bratek et al., 2015)	24 COPD 18 Control	67(7) 48 (14)	42 (17) 35 (11) Note: authors used cutoff of > 78 sec as some deficiency	$p < 0.05$
†Dal Ben & Bricolo (2012)	132 COPD	71.5 (12.1)	Age 40-49 COPD 48.9(23.6) Control 72.2 (24.9) Age 50-59 COPD 53.8 (26.3) Control 73.7 (34.5)	$p < 0.015$ $p < 0.006$
†Dal Negro, et al. (2014)	161 COPD 151 Control	Age ranked: 40-49 13 COPD 52 Control 50-59 24 COPD 52 Control 60-69 56 COPD 39 Control 70-79 68 COPD 10 Control	 73.2 (15.3) 48.9 (23.6) 96 (55.3) 53.8 (26.3) 99.9 (58.3) 67.3 (28.7) 110.1 (44.3) 84.6 (23.8)	 $p = 0.002$ $p = 0.001$ $p = 0.001$ $p = 0.004$
†Favalli, et al. (2008)	21 COPD 20 Control	74.6 (5.4) 73.7 (4.5)	92 (24-152) ** 48 (26-184) **	$p < 0.01$

Hjalmarsen et al. (1999)	10 COPD 10 Control	65.9 (7.3) 66.1(4.7)	66 (24.9) 42.2 (13.3)	p = 0.02
Kozora et al. (2005) *LVRS COPD and Controls at baseline were selected for analysis	19 COPD LVRS 20 COPD †MT 39 control	64.8(4.9) 64.3(6.2) 64(5.4)	42.4 (17) 37.6 (14.9) 30.9 (10.8)	NS
Kozora, et al. (2010)	56 COPD 54 Control	64.8 (5.9) 64.2 (5.8)	40.2 (15.8) 32.1 (12.7)	Not reported
†Liesker, et al. (2004)	30 COPD 20 Control	64.8 (8.2) 65.6 (11.2)	48 (25-173) ** 40 (22-74) **	NS
Prigatano, et al. (1983)	100 COPD 25 Control	61.5 (7.4) 59.6 (9)	46.8 (18.6) 44.6 (18.9)	NS
Seashore Rhythm Test Requires the discrimination between like and unlike pairs of musical beats Lower score indicates poorer cognitive performance				
†Grant et al., (1982)	51 COPD 51 Control	64.4 (8.1) 64.3 (10.5)	23 (n.r.) 23.5 (n.r.)	Not reported
†Hjalmarsen et al (1999)	10 COPD 10 Control	65.9 (7.3) 66.1 (4.7)	18.6 (4) 23.2 (3.8)	p = 0.02
†Prigatano et al. (1983)	100 COPD 25 Control	61.5 (7.4) 59.6 (9)	23.3 (4.3) 24.2 (3.3)	NS
Digit Vigilance Time Measure of sustained visual attention Higher score indicates poorer cognitive performance				
†Kozora et al. (2005)	19 COPD LVRS 20 COPD MT 39 control	64.8(4.9) 64.3(6.2) 64(5.4)	442.3 (90.7) 422.5 (63.0) 407.4 (70.5)	NS
†Kozora et al, (2010)	56 COPD 54 Control	64.8 (5.9) 64.2 (5.8)	435.4 (92.6) 403.4 (70.6)	NS

Barrage -must cross all lines that are randomly arranged on page Lower score indicates poorer cognitive performance				
†Incalzi, et al. (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	132 (71) 145 (78)	NS
Attention Network Test Computerized testing				
†Klein, et al. (2010)	60 COPD 60 Control	63.2 (9.8) 63.5(8.3)	Attention Network Relative alerting Relative orienting Relative conflict	 $p < 0.01$ $p < 0.05$ NS
Zahlenverbindungstest -computerized test of attention Lower score indicates poorer cognitive performance				
†(Kotterba et al., 1998)	32 COPD 10 Control	57.4(8.2) 48 (9.9)	Alertness COPD 23.1 (20.2) Control 75.5(24.1) Selective attention COPD 45.4(33.4) Control 77.0 (10.6) Divided attention COPD 46.1 (27.8) Control 35 (15.1) Continuous attention COPD 18.9 (17.2) Control 64.4 (24.4) Vigilance COPD 71.5 (20.5) Control 74.8 (16.9)	$p < 0.001$ $p \leq 0.001$ NS $p < 0.001$ NS

**reported in median and range
† Not included in meta-analysis

APPENDIX L

Memory and Learning Studies

Table 16 L. 1 Memory and Learning Studies

Study	Sample	Mean Age (SD)	Mean (SD)	Sign.
Span Forward -measures short term memory span Called digit when numbers are used and verbal is words are used Lower number indicated less memory span				
†Cleutjens et al., (2014)	5764 COPD 37,275 Controls	9 (7.6) 56 (8.3)	**Digit** β=-0.05 (-0.10-.00) **	p =0.47
†Incalzi, et al., (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	**Verbal** 5.1 (0.9) 5.7 (0.9)	NS
Incalzi, et al (1997)	42 COPD 27 Control	72 (62-76) ** 70 (67-72) **	**Digit** 5.1 (0.9) 5.4 (0.9)	NS
Kozora, et al., (1999)	32 COPD 31 Control	70.3 (4.4) 69.9(5.8)	**Digit** 7.2 (1.4) 6.7 (1.0)	NS
Kozora et al. (2005) *LVRS COPD pts and controls at baseline were selected for analysis	19 COPD LVRS 20 COPD †MT 39 control	64.8(4.9) 64.3(6.2) 64(5.4)	**Digit** 14.7 (3.4) 14.2 (2.7) 16.1(4.1)	NS
Kozora et al., (2010)	56 COPD 54 Control	64.8 (5.9) 64.2 (5.8)	**Digit** 14.1 (2.9) 15.5 (4.2)	NS
Ortapamuk & Naldoken (2006)	10 non-hypoxemic COPD 8 stable hypoxemic COPD 10 Control	54.8(6.9) 52.6(5.4) 54.1(8.7)	**Digit** 6.9 (1.7) 7.0 (0.9) 7.1 (5.1)	NS
Pereira, et al. (2011)	34 COPD 18 Control	65.2 (7) 62.7 (4)	**Digit** 10.7 (2.8) 11.7 (3.8)	NS

Zhang, et al. (2013)	25 COPD 25 Control	69.2 (8) 68(8)	**Digit** 7.0 (1.6) 7.7 (1.4)	NS
Wechsler Memory Scale Lower score indicates poorer cognitive performance				
Dodd et al., (2013)	50 COPD 30 Control	69 (8) 65 (8)	**Verbal** **Immediate** COPD: 8.9 (2.7) Control: 11.2 (3.8) **Delayed** COPD: 11.5 (2.3) Control: 12.1 (2.7)	p < .001 p = .007
†Grant et al., 1982	51 COPD 51 Controls	64.4 (8.1) 64.3(10.5)	**Immediate** COPD: 20.1 % loss Control: 17.2 % loss **Delayed (30 min)** COPD: 33.3 % loss Control: 20.2 % loss	NS p < .05
Incalzi, et al. (1997)	42 COPD 27 Control	72 (62-76) 70 (67-72)	**Immediate** COPD 33.6 (7.3) Control 40.5 (6.8) **Delayed** COPD 6.2 (2.5) Control 8.6 (2.9)	p<0.001 p<0.001
Kozora et al., (1999)	32 COPD 31 Control	70.3 (4.4) 69.9(5.8)	**Immediate** COPD 16.0 (3.8) Control 19.4(3.1) **Delayed** COPD 6.7 (1.3) Control 7.3 (0.8)	NS NS
Ortapamuk & Naldoken (2006)	†10 non-hypoxemic COPD 8 stable hypoxemic COPD 10 controls	54.8(6.9) 52.6(5.4) 54.1(8.7)	**Immediate** Non-hypoxemic COPD 33.8 (3.7) Stable hypoxemic COPD 27.1 (5.9) Control 35.2 (8.3) **Delayed** Non-hypoxemic COPD 7.8 (2.9) Stable hypoxemic COPD 4.1 (2.7) Control 8.6 (3.1)	NS p<0.01 between hypo-xemic and controls
†Zhou et al (2012)	110 COPD	80.9(1.78)	**Visual** **Immediate** COPD 16.1 (2.89)	p = 0.018

	110 Control	80.8 (1.59)	Control 17.0 (2.61) **Delayed** COPD 5.2 (1.18) Control 5.5 (1.29)	 NS
Raven's colored Progressive Matrices Immediate Visual Memory & Visual-Spatial Intelligence Lower score indicates poorer cognitive performance				
†Favalli, et al. (2008)	21 COPD 20 Control	74.6 (5.4) 73.7 (4.5)	41.8 (23.8-53) ** 50.5 (32.8-57.3) **	p<0.001
†Incalzi, et al. (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	23 (4.8) 27 (4.5)	p<0.001
†(Ortapamuk & Naldoken, 2006)	†10 non-hypoxemic COPD 8 stable hypoxemic COPD 10 controls	54.8(6.9) 52.6(5.4) 54.1(8.7	15.4 (5.5) 14.8 (4.5) 17.2 (5.1)	 NS
Wechsler Adult Intelligence Scale Subtest Block Design -recreate red and white blocks measured in speed and accuracy Lower scores indicate poorer performance				
†Hjalmarsen et al. (1999)	10 COPD 10 Control	65.9 (7.3) 66.1 (4.7)	21.6 (6.2) 28.5 (6.3)	p = 0.02
Wechsler Memory Scale-Revised Has 7 subsets that require the performance of a specific variety of tasks and to retell certain details Lower score indicates poorer cognitive performance				
†Hjalmarsen et al., (1999)	10 COPD 10 Control	65.9 (7.3) 66.1 (4.7)	WMS-R Subset **Verbal paired associates – immediate** COPD 12.5 (4.9) Control 17.9 (2.5) **WMS-R Subset Visual Reproduction immediate** COPD 24.2 (7.9) Control 33.1 (9.9) **WMS-R Subset Verbal paired associates –delayed** COPD 4.4 (2) Control 6.8 (1) **WMS-R Subset Visual**	 p = 0.006 p = 0.04 p = .003 p = 0.02

			Reproduction delayed COPD 19.6 (8.1) Control 28.4 (7.4)	
†Kozora et al. (2002)	29 COPD 21 Control	66.9 (n.r.) 65.2 (n.r.)	**Story Retention** COPD 79.3 (2.9) Control 82.4 (2.7) **Visual Retention** COPD 69.8 (4.9) Control 69 (5.7) **Verbal Pairs** COPD 17.5 (0.7) Control 19 (0.7)	Not reported
†Prigatano et al., (1983)	100 COPD 25 Control	61.5 (7.4) 59.6 (9)	WMS-R Subset **Verbal paired associates – immediate** COPD 8.0 (1.5) Control 8.8 (1.5) **WMS-R Subset Visual Reproduction immediate** COPD 6.7 (3.3) Control 9.1 (2.2) **WMS-R Subset Verbal paired associates –delayed** COPD 7.5 (1.7) Control 8.3 (1.2) **WMS-R Subset Visual Reproduction delayed** COPD 5.7 (3.3) Control 8.0 (2.9)	p =.03 p = .001 p = .04 p = .002
†Shim et al. (2001)	15 COPD	62(4)	WMS-R **General memory** 62 (15) 100 (15) * **Verbal memory** 66 (14) 100 (15) * **Visual memory** 71 (21) 100 (15) * **Delayed memory** 67 (13)	Not reported Note: data missing from 2 subjects

			100 (15)*	
†Zhang et al (2013)	25 COPD 25 Control	69.2 (8) 68(8)	WMS-R **Visual Reproduction** COPD 8.2 (3.4) Control 10.3 (3.0) **Figure Memory** COPD 10.5 (3.0) Control 12.4 (1.9)	 P = 0.031 P = 0.010
Corsi Block – Spatial Span Involves mimicking a researcher as he taps a sequence of up to 9 blocks Lower score indicates poorer cognitive performance				
†Incalzi, et al (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	4.5 (0.7 5.3 (0.9)	NS
Rey Auditory Verbal Learning Test (RAVLT) A list of 15 words are heard and then as many as possible are recalled Lower score poorer cognitive performance				
†Favalli et al. (2008)	21 COPD 20 Control	74.6 (5.4) 73.7 (4.5)	**Rey's immediate** COPD 37.6 (29.2-59) ** Control 43.5 (33-67) ** **Rey's List Delayed** COPD 8.3 (3.1-13.6) ** Control 10.4 (7.4-15.8) **	p <0.02 p<0.001
†Incalzi et al., (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	**RAVLT short-term** COPD 33 (7.3) Control 41 (7) **RAVLT long-term** COPD 5.4 (2.5) Control 8.7 (3)	 p <0.001 p < 0.005
†Pereira et al., (2011)	34 COPD 18 Control	65.2 (7) 62.7 (4)	**RAVLT A1-5** COPD 43.5 (10) Control 50.5 (10) **RAVLT SDFR** COPD 7.5 (3.3) Control 10.7 (3.6) **RAVLT LDFR** COPD 8.4 (3.8) Control 11.6 (3.9)	p = 0.03 p =0.002 p = 0.003
Wechsler Memory Scale III-logical memory Lower score indicates poorer cognitive performance				
†Borson, et al. (2008)	18 COPD:	68.5 (8)	COPD non-02 dependent 12.6 (2.1)	p = 0.049

	(9 02 dependent, 9 without 02) 9 Control	68.2 (5.8)	COPD 02 dependent 10.7 (3.1) Control 13.7 (2.1)	*02 uses lower than both groups (p=0.5 -1)
Priganto et al., (1983)	100 COPD 25 Control	61.5 (7.4) 59.6 (9.0)	**Immediate** COPD 18.1 (6.4) Control 20.9 (5.4) **Delayed** COPD 14.9 (6.6) Control 18.7 (5.8)	p = .04 p = .009
Story Recall				
†Liesker et al., (2004)	30 COPD 20 Control	64.8 (8.2) 65.6 (11.2)	**Direct** COPD 18 (3-20) ** Control 18 (3-20) ** **Delayed** COPD 18 (0-20) ** Control 18 (0-20) **	NS NS
Verbal and Non-verbal Learning from the Vienna Test System A computer assisted application Lower score indicates poorer cognitive performance				
†Incalzi et al. (1997)	42 COPD 27 Control	72 (62-76) 70 (67-72)	40.5 (16.5) 47.3 (16.6)	NS
†Klein et al., (2010)	60 COPD 60 Control	63.2 (9.8) 63.5 (8.3)	**Diff corr/false** COPD 23.8 (20.3) Control 50 (10) **VLT Corr** COPD 40.9 (25.6) Control 50 (10) **False** COPD 35.6 (32.6) Control 50 (10) **Diff corr/false** COPD 1.9 (27.1) Control 50 (10) **NVLT Corr** COPD 55.7 (25.7) Control 50 (10) **False** COPD 21.3 (24.6) Control 50 (10)	p < 0.05 p < 0.05 p < 0.01 NS p < 0.01 p < 0.01
Prospective Memory				

†Cleutjens et al. (2014)	5764 COPD 37275 Controls	59(7.6) 56 (8.3)	β = -0.15 (-0.22 to 0.009)	p<0.005
Visual Spatial Memory Lower score indicates poorer cognitive performance				
†Cleutjens et al (2014)	5764 COPD 37,275 Controls	59 (7.6) 56 (8.3)	**Round 1** β = 0.06 (0.03-0.10) **Round 2** β = 0.09 (0.00-0.18)	p<0.05 p=0.047
†Dodd et al., (2013)	50 COPD 30 Control	69(8) 65(8)	8.2 (2.8) 10(0)	p<0.001
†Incalzi et al (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	**Spatial span forward** COPD 4.5 (0.7) Control 5.3 (0.8 **Spatial span reverse** COPD 3.8 (0.6) Control 4.4 (0.7)	 NS p<0.005
Rey Complex Figure Test Measure visuospatial ability and visuospatial memory Score is based on three drawing trials: copy, 3-minute immediate recall and 30-minute delayed Lower score indicates poorer cognitive performance				
†Dodd, et al. (2013)	50 COPD 30 Control	69 (8) 65 (8)	**Immediate** COPD 9.4 (4.3) Control 11.3 (4.7) **Delayed** COPD 9.4 (4.4) Control 11.4 (4.8)	. NS NS

* standardized norm
** reported median and range
† Not included in meta-analysis

APPENDIX M

Executive Function Studies

Table 17 M. 1 Executive Function Studies

Study	Sample	Mean Age (SD)	Mean (SD)	Sign.
Verbal Fluency Say as many words possible from a given category Lower score indicates poorer cognitive performance				
Incalzi et al., (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	**Phonetic** COPD 24.2 (9.7) Control 31 (8) **Semantic** COPD 19.8 (5) Control 24 (7)	p < 0.005 NS
†Dodd, et al. (2013)	50 COPD 30 Control	69 (8) 65 (8)	**Delis-Kaplan Verbal fluency** COPD 11.1 (3.7) Control 12 (3.4)	NS
†Favalli et al. (2008)	21 COPD 20 Control	74.6 (5.4) 73.7 (4.5)	**Phonemic** COPD 30.5 (18-47) *** Control 36.5 (16-53) *** **Semantic** COPD 11.8 (6.7-17.3) *** Control 14.7 (9.5-18.5) ***	NS p < 0.05
Kozora, et al., (1999)	32 COPD 31 Control	70.3 (4.4) 69.9(5.8)	**Letter Fluency** COPD 36.4 (11.4) Control 46.3 (13.4) **Animal Fluency** COPD 19.3 (5.1) Control 19.0 (4.3)	p < 0.001 NS
†Kozora et al., (2002)	9 COPD 21 Control	66.9 65.2	Note: from Controlled Oral Word Association Test **Letter Fluency** 31.2 (1.9) 41.4 (3.1)	
Kozora et al. (2005) *LVRS COPD pts and Controls were selected at baseline for analysis	19 COPD LVRS 20 COPD †MT 39 Control	64.8(4.9) 64.3(6.2) 64(5.4)	**Letter Fluency** COPD LVRS 31.6 (10.7) COPD †MT 31.1 (10) Control 40.2 (12.4) **Animal Fluency** COPD LVRS	NS NS

			19.3 (4.3) COPD †MT 19.7 (4.5) Control 19.3 (4.4) (at baseline)	
Kozora et al. (2010)	56 COPD 54 Control	64.8 (5.9) 64.2 (5.8)	**Letter Fluency** COPD 31.6 (10.5) Control 38.9 (12.1) **Animal Fluency** COPD 19.2 (4.4) Control 19.2 (4.3)	Not reported
Ortapamuk & Naldoken (2006)	†10 non-hypoxemic COPD 8 stable hypoxemic 10 Control	54.8(6.9) 52.6(5.4) 54.1(8.7)	**Phonological** †non-hypoxemic COPD 26.8 (8.8) stable hypoxemic COPD 25.9 (7.8) Control 27.8 (9.1)	NS
Pereira, et al. (2011)	34 COPD 18 Control	65.2 (7) 62.7 (4)	**Letters FAS Fluency** 21.1(1) 30.2 (12.3	p = 0.003
Span Backwards – Executive Function Numbers that are read must be repeated backwards starting with last number Lower score indicates poorer cognitive performance				
Incalzi, et al., (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	3.3 (0.9) 4.1 (0.8)	p < 0.05
Incalzi, et al., (1997)	42 COPD 27 Control	72 (62-76) 70 (67-72)	3.3 (0.98) 3.8 (0.8)	p < 0.001
Kozora, et al., (1999)	32 COPD 31 Controls	70.3 (4.4) 69.9(5.8)	5.4 (1.4) 5.2 (1.4)	NS
Ortapamuk & Naldoken (2006)	†10 non-hypoxemic COPD 8 stable hypoxemic COPD 10 Control	54.8(6.9) 52.6(5.4) 54.1(8.7)	†non-hypoxemic COPD 5.1 (1.1) stable hypoxemic COPD 4.8 (1.3) Control 5.3 (0.8)	NS
Zhang et al (2013)	25 COPD 25 Control	69.2 (8) 68(8)	4.1 (1.9) 4.3 (1.5)	NS
Trailmaking Test B Consists of 25 circles containing letters and numbers which need to be alternately connected in ascending order (ex. A 1 B 2) -results are recorded in number of seconds taken to complete task -a higher score indicates poorer cognitive function				
†Bratek, et al. (2013)	12 COPD 13 Controls	67 48	107.79(n.r.) 67.37 (n.r.)	Not reported

Bratek, et al. (2015)	24 COPD 18 Controls	67(7) 48(14)	107 (41) 70 (23)	p < 0.05
†Dal Ben & Bricolo (2012)	132 COPD COPD Control	71.5 (12.1) 40-49	11.8 (53.9) *** 163.2 (97.5) ***as reported in results	p < 0.015
†Dal Negro, et al. (2014)	16 COPD 52 Control 27COPD 52 Control 25COPD 39 Control 30 COPD 10 Control	40-49 50-59 60-69 70-79	157.3 (53.9)3) 111.8 (53.9) 184.2 (101.9) 134.5 (80.1) 186.7 (100.3) 164.5 (97.4) 254.6 (197.8) 336.8 (197.8)	p = 0.01 p = 0.01 NS NS
†Favalli, et al. (2008)	21 COPD 20 Control	74.6 (5.4) 73.7 (4.5)	143 (55-346) *** 68.5 (11-270) ***	p < 0.01
†Grant, et al. (1982)	51 COPD 51 Control	64.4 (8.1) 64.3 (10.5)	161.8 (not reported) 119.8 (not reported)	p < 0.001
Hjalmarsen, et al. (1999)	10 COPD 10 Control	65.9 (7.3) 66.1 (4.7)	201.9 (97.2) 98.1 (29.6)	p = 0.005
Kozora, et al. (1999)	32 COPD 31 Control	70.3 (4.4) 69.9(5.8)	108.8 (49.7) 93.9 (48)	NS
Kozora, et al. (2002)	29 COPD 21 Control	66.9(n.r.) 65.2 (n.r.)	125.5(15.2) 72 (4.2)	Not reported
Kozora et al. (2005) *LVRS COPD pts at baseline were selected for analysis	19 COPD LVRS 20 COPD †MT 39 Control	64.8(4.9) 64.3(6.2) 64(5.4)	102.4 (38) 113.9 (69.7) 79.9 (25.5)	Not reported
Kozora, et al. (2010)	56 COPD 54 Control	64.8 (5.9) 64.2 (5.8)	107 (49.5) 80.7 (24.8)	Not reported
†Liesker, et al. (2004)	30 COPD 20 Control	64.8 (8.2) 65.6 (11.2)	122 (54-235) *** 89 (41-163) ***	p < 0.05
Prigatano, et al. (1983)	100 COPD 25 Control	61.5 (7.4) 59.6 (9)	125.1 (62) 103.8 (35.5)	p = .03
†Shim, et al (2001)	15 COPD	62(4)	CTT1 35 (11) ** 50 (10) **	Not reported

	Standardized value =100		CTT2 35 (14) ** 50 (10) **	
Corsi Block – Reverse Spatial Span				
Incalzi, et al. (1993)	36 COPD 29 Control	69 (10) 68.9 (7.7)	3.8 (0.6) 4.4 (0.7)	p < 0.005
Copying Designs				
Incalzi, et al., (1993)	36 COPD 29 controls	69 (10) 68.9 (7.7)	**Simple copy** COPD 6.9 (2.3) Control 8.8 (2) **Copy with landmarks** COPD 61 (6) Control 65 (4)	 p < 0.001 p < 0.005
Ortapamuk & Naldoken (2006)	†10 non-hypoxemic COPD 8 stable hypoxemic COPD 10 Control	54.8(6.9) 52.6(5.4) 54.1(8.7)	non-hypoxemic COPD 7.0 (3.6) stable hypoxemic COPD 6.9 (3.0) Control 7.2 (2.8) **Copy with landmarks** non-hypoxemic COPD 60.1 (8.9) stable hypoxemic COPD 59.6 (7.5) Control 61.6 (5.2)	NS NS
Standard Progressive Matrices (SPM)				
†Klein et al (2010)	60 COPD 60 Control	63.2 (9.8) 63.5(8.3)	9.9 (13.2) 50 (10)	p < 0.01
Fluid intelligence Problem Solving and reasoning ability				
†Cleutjens et al., (2014)	5764 COPD 37,275 Control	59 (7.6) 56 (8.3)	β = -0.05 (-0.11-.003)	NS
WAIS Similarities				
†Hjalmarsen et al (1999)	10 COPD 10 Control	65.9 (7.3) 66.1 (4.7)	14.8 (4.3) 15.1 (4.6)	NS
†Kozora et al. (2005) *LVRS COPD pts at baseline were selected for analysis	19 COPD LVRS 20 COPD †MT 39 control	64.8(4.9) 64.3(6.2) 64(5.4)	16.5 (5.1) 16.6 (6.8) 19.1 (3.7)	Not reported
†Kozora et al. (2010)	56 COPD 54 Control	64.8 (5.9) 64.2 (5.8)	16.8 (5.5) 19.8(3.7)	Not reported

**reported standardized scores
***reported median and range
†not included in meta-analysis

APPENDIX N

Language Studies

Table 18 N. 1 Language Studies

Study	Sample	Mean Age (SD)	Mean (SD)	Sign.
Aphasia Screening Test Series of tasks that require one to name objects spell words, identify numbers				
†Grant et al., 1982	51 COPD 51 Control	64.4 (8.1) 64.3 (10.5)	7.8 (n.r.) 6.6 (n. r.)	NS
†Prigatano et al. (1983)	100 COPD 25 Controls	61.5 (7.4) 59.6 (9)	7.6 (7.3) 3.7 (4.1)	P = .0006
Boston Naming 15 Measures visual confrontation naming abilities of 15 words Lower score indicates poorer cognitive performance				
Kozora, et al., (1999)	32 COPD 31 Control	70.3 (4.4) 69.9(5.8)	13.9 (1.5) 13.9 (1.2)	NS
Kozora et al. (2005) *LVRS COPD pts at baseline was selected for analysis	19 COPD LVRS 20 COPD †MT 39 Control	64.8(4.9) 64.3(6.2) 64(5.4)	13.7 (1.8) 13.4 (2.1) 14.2 (1.1)	NS
Kozora et al., (2010)	56 COPD 54 controls	64.8 (5.9) 64.2 (5.8)	13.6 (1.8) 14.4 (2.9)	NS

APPENDIX O

Processing Speed Studies

Table 19 O. 1 Processing Speed Studies

Study	Sample	Mean Age (SD)	Results Mean (SD)	Sign.
Simple Reaction Time Higher score indicates poorer cognitive performance				
†Cleutjens et al., (2014)	5764 COPD 37,275 Control	59 (7.6) 56 (8.3)	β = 4.62 (1.25-8.01)	 P =007
†Hjalmarsen et al (1999)	10 COPD 10 Control	65.9 (7.3) 66.1 (4.7)	400.9 (91.8) 329.1(65.6)	NS
Complex Reaction Time Higher score indicates poorer cognitive performance				
†Hjalmarsen et al (1999)	10 COPD 10 Control	65.9 (7.3) 66.1 (4.7)	543.4 (146.5) 416.7 (42.6)	p = 0.02
Complex Reaction Time, sequential Higher score indicates poorer cognitive performance				
†Hjalmarsen et al (1999)	10 COPD 10 Control	65.9 (7.3) 66.1 (4.7)	621.1 (132.1) 507.8 (64.4)	p = 0.03
Overall Reaction Time -Attention Network Test Computerized test Higher score indicates poorer cognitive performance				
†Klein et al (2010)	60 COPD 60 Control	63.2 (9.8) 63.5(8.3)	649 (113) 583 (110)	p < 0.01
Digit Symbol (from WAIS-III) Timed test that requires matching 9-digit symbols with their corresponding number Lower score indicates poorer cognitive performance				
Borson, et al. 2008	18 COPD: 9 non-oxygen dependent COPD & 9 02 dependent 9 Control	 68.5 (8) 68.2 (5.8)	COPD non-oxygen dependent 12.1 (1.5) 02 dependent 8.4(3.3) Control 12.7 (1.5)	p=0.034 02 users lower scores than both other groups p ≤0.005

Dodd, et al. (2013)	50 COPD 30 Control	69 (8) 65 (8)	96 (14) 111(13)	p<0.001
†Favalli et al. 2008	21 COPD 20 Control	74.6 (5.4) 73.7 (4.5)	17 (9-35) ** 24 (12-45) **	p<0.001
Kozora et al. (2005) *LVRS COPD pts was selected for analysis	19 COPD LVRS 20 COPD †MT 39 control	64.8(4.9) 64.3(6.2) 64(5.4)	40.9 (5.2) 44.2 (9.2) 51.4 (10)	NS
Kozora et al. (2010)	56 COPD 54 Control	64.8 (5.9) 64.2 (5.8)	42.6(8.5) 51.1(10.3)	NS
†Liesker et al., (2004)	30 COPD 20 Control	64.8 (8.2) 65.6 11.2)	34.5 (15-60) ** 47 (24-75) **	p < 0.05
Prigatano et al., (1983)	100 COPD 25 Control	61.5 (7.4) 59.6 (9)	6.4 (2.0) 8.0 (2.5)	P = .001

**reported median and range
†not included in meta-analysis

APPENDIX P

Selected HRS Measures

Table 20 P. 1 Selected HRS Measures

Questions	Response Options
Demographics	
-Age	Enumerated
-Year of birth	
-Gender	
-Education Level Did you get a high school diploma or pass a high school equivalency test? Did you get a college degree? What is the highest degree you have earned	 1=Yes, diploma; 3= Yes, equivalency; 5=no; 8=DK; 9=RF 1=Yes; 5=no; 8=DK; 9=RF 1=less than bachelors; 2=bachelors; 3=masters 4=law; 5=Ph.D.; 6=MD; 7=other; 8=DK; 9=RF
-Household Income	Enumerated
-Net Worth	Enumerated
-Marital Status	
-**Smoking history** -ever smoked -smoke now -number of packs per day -age started smoking	
-Comorbities -Has your doctor ever told you that you have. . . -high blood pressure or hypertension? -diabetes? -cancer? -heart condition? -stroke? -emotion/psychiatric problems? -arthritis?	
Cognition **Immediate Recall** Respondent is given list of 10 nouns and asked to recall as many as possible in any order **Delayed Recall** After approximately 5 minutes is asked to recall the nouns previously presented Executive function **Serial 7s Test**	 Number correct Number correct

Subtract 7 from 100 and continue subtracting 7 from each subsequent number for a total of 5 trials. **Backwards Count starting from 20** Count backwards for 10 continuous numbers.	Number correct Completed on 1st attempt =1 2nd attempt =2 Unable to complete = 0
Sleep How often do you have trouble falling asleep? How often do you have trouble staying asleep? How often do you have trouble with waking up too early and not being able to fall asleep again? How often do you feel really rested when you wake up in the morning?	Would you say most of the time, sometimes, or rarely or never? Recoded to any difficulty =1 No difficulty = 0 Composite score
Emotional State **Depression** -20 items from CEDS **Anxiety** Have you ever had an anxiety disorder?	1=yes, 0 = no
Life Satisfaction Please think about your life as a whole. How satisfied are you with it? Are you completely satisfied, very satisfied, somewhat satisfied, not very satisfied, or not at all satisfied?	1. Completely Satisfied 2. Very Satisfied 3. Somewhat Satisfied 4. Not Very Satisfied 5. Not at All Satisfied 8. DK (Don't Know); NA (Not Ascertained) 9. RF (Refused)
Functional Performance	
Walking several blocks Walk one block Climbing several flights of stairs Climb one flight of stairs Walk across the room	Mobility Score range 0-5
Sitting for about 2 hours Getting up from a chair Stooping, kneeling or crouching Pull or push large object	Large Muscle groups Score range 0-4
Walking 1 block Walk across the room Climbing a flight of stairs Bathing Transfer to bed	Gross Motor Skills Score range 0-5
Picking up a dime Dressing Eating	Fine Motor Skills Score range 0-3
Need for cognition	
1) I like to have the responsibility of handing a situation that requires a lot of thinking.	1=Not at all like me 2=Somewhat like me 3=Uncertain

2) I really enjoy a task that involves coming up with new solutions to problems. 3) The notion of thinking abstractly is appealing to me. 4) I would rather do something that requires little thought than something that is sure to challenge my thinking abilities. (-) 5) I try to anticipate and avoid situations where there is likely a chance I will have to think in depth about something (-). 6) I only think as hard as I have to (-).	4=Somewhat like me 5=Very much like me. Cognitive Enjoyment (Positive Items 34a_a, b, and c) Cognitive Effort (Reverse coded Items 34a_d. e. and f). Composite Score
Perceived mastery	
I can do just about anything I really set my mind to. When I really want to do something, I usually find a way to succeed at it. Whether or not I am able to get what I want is in my own hands. What happens to me in the future mostly depends on me. I can do the things that I want to do.	6-point Likert scale Scale score
Hopelessness	
I feel it is impossible for me to reach the goals that I would like to strike for. The future seems hopelessness to me and I can't believe that things are changing for the better. I don't expect to get what I really want. There's no use in really trying to get something I want because I probably won't get it.	6-point Likert scale 1 strongly disagree to 6 strongly agree Composite score
Satisfaction with aging	
The next statements are about the way people feel about their age and about the things that happen as they get older. Please tell us how much you agree or disagree with each statement for you personally.) 1) Things keep getting worse as I get older. 2) I have as much as pep as I did last year. 3) The older I get, the more useless I feel. 4) I am as happy now as I was when I was younger. 5) As I get older, things are better than I thought they would be. 6) So far, I am satisfied with the way that I am aging. 7) The older I get, the more I have had to stop the things that I liked. 8) Getting older has brought with it many things that I do not like.	6-point Likert scale Create a rating of aging satisfaction by reverse coding items Q29b1, b3, b7, and b8 and averaging the scores across all 8 items. Alternatively, separate scores may be obtained for positive and negative aging satisfaction. Average across items Q29 b2, b4, b5, and b6 to get a rating of positive aging satisfaction. Average across items Q29 b1, b3, b7, and b8 to get a rating of negative aging satisfaction

Appendix Q

Sample Size from HRS Data Set for Longitudinal Study Based on Assessment Point

Table 21 Q. 1 Sample Size from HRS Data Set for Longitudinal Study Based on Assessment Point

Assessment point	Sample Size Non-COPD	Years with COPD	Sample Size COPD
1	3070	1	380
2	3070	3	332
3	3070	5	289
4	3070	7	233
5	3068	9	172
6	3070	11	134
7	3070	13	95
8	3068	15	56
9	3066	17	30
10	3060	19	14

APPENDIX R

Regression of Psychosocial Variables on Domains of Cognition Cross-sectional Study from 2014 Wave of HRS Data Set

Table 22 R. 1 Regression of Psychosocial Variables on Domains of Cognition Cross-sectional Study from 2014 Wave of HRS Data Set

Attention/Executive Function: Serial Seven Subtractions Non-COPD N =1285 $F(4, 1280) = 10.80$, $p < 0.01$, $R^2 = 0.03$			
	β Coef.	t-score	p-value
Need for Cognition	-0.398	-2.90	0.004
Mastery	-0.012	-1.20	NS
Hopelessness	-0.047	-3.87	0.000
Satisfaction With Aging	0.012	1.71	NS
Constant (Seven)	4.57		
Memory & Learning Immediate Recall COPD N = 143 $F(4,138) = 4.29$, $p < 0.01$, $R^2 = 0.11$			
Need for Cognition	-0.055	-1.31	NS
Mastery	0.0157	0.52	NS
Hopelessness	-0.122	-3.30	0.001
Satisfaction With Aging	-0.02	-1.00	NS
Constant (Immediate)	7.34		
Memory & Learning Immediate Recall Non-COPD N = 1285 $F(4,1280) = 15.59$, $p < 0.001$, $R^2 = 0.04$			
Need for Cognition	-0.24	-1.81	NS
Mastery	-0.015	-1.46	NS
Hopelessness	-0.061	-5.01	0.00
Satisfaction With Aging	0.019	2.65	<0.001
Constant (Immediate)	5.9		
Memory & Learning Delayed Recall COPD N = 143 $F(4,138) = 15.19$, $p < 0.001$, $R^2 = 0.12$			
Need for Cognition	-0.05	-.99	NS
Mastery	0.008	0.24	NS
Hopelessness	-0.167	-3.77	0.00

Satisfaction With Aging	-0.23	-0.98	NS
Constant (Immediate)	6.9		
Memory & Learning Delayed Recall Non-COPD N = 1285 $F(4,1280) = 46.74$, $p<0.001$, $R^2 = 0.04$			
Need for Cognition	-0.034	-2.17	0.03
Mastery	-0.012	0.335	NS
Hopelessness	-0.071	-4.92	0.00
Satisfaction With Aging	0.018	2.21	NS
Constant (Immediate)	5.07		

APPENDIX S

Convergent and Discriminant validity of NIHTB-CB Persons Aged 8-85 (Weintraub et al., 2014)

Table 23 S. 1 Convergent and Discriminant Validity of the NIHTB-CB Persons Aged 8-85

Cognitive Battery Measures	Convergent Test	Convergent Validity		Discriminant Test	Discriminant Validity	
		N	r		N	r
Flanker/ Attention, Executive	Wechsler Adult Intelligence Scale	317	-0.48[b]	Peabody Picture Vocabulary Test	89	0.15[a]
Dimension Change Card Sort/ Executive Switching	Delis-Kaplan Executive Function	317	-0.51[a]	Peabody Picture Vocabulary Test	85	0.14[c]
Picture Sequence Memory/ Episodic Memory	Brief Visuospatial Memory Test-revised	350	0.69[a]	Peabody Picture Vocabulary Test	115	-0.08
Vocabulary/Language	Peabody Picture Vocabulary Test	351	0.78[a]	Brief Visuospatial Memory Test-revised	111	0.08
Reading/ Language	Wide Range Achievement Test	351	0.93[a]	Brief Visuospatial Memory Test-revised	115	0.19[a]
Pattern Comparison/ Processing Speed	Wechsler Intelligence Scale	349	0.49[a]	Peabody Picture Vocabulary Test	99	0.12[c]
List Sorting/ Working Memory	Wechsler Intelligence Scale	350	0.58[a]	Peabody Picture Vocabulary Test	112	0.30[a]

[a] $p<0.001$
[b] $p < 0.01$
[c] $p < 0.05$

APPENDIX T

Reliability NIHTB-CB

Table 24 T. 1 Reliability of NIHTB-CB

Cognitive Domain	**NIH toolbox measurement(s)**	**Reliability 7-21-day test-retest**
Attention	NIH Toolbox Flanker Inhibitory Control and Attention Test	r = 0.85 CI (0.74-89).
Executive Function	NIH Toolbox Flanker Inhibitory Control and Attention Test NIH Toolbox Dimensional Change Card Sort Test	r = 0.85 with CI (0.74-0.89) r = 0.88 with CI (0.82-0.92)
Working memory	NIH Toolbox List Sorting Working Memory Test	r = 0.77 CI (0.67-0.84)
Language	NIH Toolbox Picture Vocabulary Test Oral Reading Recognition Test	r = 0.81 CI (0.73-0.87)
Processing speed	NIH Toolbox Pattern Comparison Processing Speed Test	r = 0.72 CI (0.60-0.81)
Episodic Memory	NIH Toolbox Picture Sequence Memory Test	r = 0.77 CI (0.67-0.84).

(NIH Toolbox.org).

APPENDIX U

Feasibility and Acceptability Survey

Table 25 U .1 Feasibility and Acceptability Survey

	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
I received adequate instruction to complete the task.					
The screen was easy to read.					
Answering the questions using a computer keyboard was easy.					
The test took too long.					
I needed to take breaks during the test.					
My overall impression of the experience was excellent.					

If you were asked to take these tests again:

What would you like to see done differently?

What would you like to see stay the same?

APPENDIX V

Correlations of Domain-specific Cognitive Function - Spearman's rho

Table 26 V. 1 Correlations of Domain-specific Cognitive Function, Related Factors, Functional Performance, and Life Satisfaction - Spearman's rho

	Attention/ Flanker	Exec function Dimen. Sort	Episodic Memory Pict. Sequence	Language Pict. Vocab..	Language Oral	Processing Speed Pattern Recogn.	Working Memory List Sort
Physical Function	-.302	.043	-.185	.235	.119	.350	.082
Mobility	-.337	.170	-.226	.149	-.167	.244	-.020
Ability Social Participation	-.319	-.185	-.512*	.404	.106	.437	.047
Life Satisfaction	-.397	-.154	-.301	.151	.079	-.166	.327
Related Factors							
Disease Severity FEV1	-.291	.064	-.391	.229	.201	.203	-.391
mMRC	.084	.094	-.444	-.319	.062	-.444	-.035
Fatigue	.227	.012	.153	-.378	.141	-.283	-.392
Anxiety	.263	.334	.273	-.375	.035	-.143	-.211
Depression	.397	.069	.179	-.432	-.064	-.128	-.434
Sleep	-.118	.314	-.204	-.290	.150	-.351	-.663**

*$p \leq 0.05$
**$p \leq 0.00$