THE ROLES OF CARDIOVASCULAR DISEASE AND DEPRESSION IN THE RELATIONSHIP BETWEEN RESPIRATORY DISEASE AND NEUROPSYCHOLOGICAL FUNCTIONING IN OLDER ADULTS

A dissertation submitted in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

to the faculty of the

DEPARTMENT OF PSYCHOLOGY

of

ST. JOHN'S COLLEGE OF LIBERAL ARTS & SCIENCES
at
ST. JOHN'S UNIVERSITY
New York
by
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Date Submitted 9/24/2021 Date Approved 9/25/2021

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ABSTRACT

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Alexander J. Gordon

The pathophysiology of severe respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), supports the theory that oxygen deprivation to the brain may impact the brain's execution of cognitive functions. Imaging studies also suggest that neuroanatomical changes in areas of the brain responsible for cognitive processes may be associated with respiratory diseases. Research in this area has failed to conclude definitively, especially in an older adult population, which is more likely to experience comorbid depression and cardiovascular disease, universally acknowledged predictors of poorer cognitive performance, the extent of the relationship between respiratory illness and cognitive functioning. The current study investigated the association between respiratory disease with cognitive performance in older adults, also considering the relative impact of cardiovascular disease and depression. Functioning was examined globally and in the individual domains of psychomotor functioning and verbal ability. Physiological measures of disease were also explored for potential relationships with cognition. Results suggest that depression was consistently associated with poorer performance across cognitive domains, whereas cardiovascular disease was

primarily associated with reduced functioning in psychomotor tasks. After accounting for these effects, no additional association between respiratory disease and cognitive functioning was identified, with the possible exception of COPD relating to enhanced verbal ability. None of the physiological measures obtained were found to correlate with cognition in this research. Explanations and implications of these findings are discussed.

ACKNOWLEDGEMENTS

I would like to express gratitude to Dr. Robin Wellington, dissertation committee chair, for her sage advice and for providing a learning environment that did not complicate the simple things, keeping me focused on the goal with the least amount of stress as possible. I also owe gratitude to Dr. Bill Chaplin for sharing his statistical prowess and for making himself accessible despite wearing many hats. I am fortunate to have experienced him as a professor, mentor, and member of this dissertation committee. Another committee member, Dr. Jeffrey Nevid, deserves a shout-out for sharing a record number of "multiple relationships" with me. It was no easy task serving as my research fellowship supervisor for 4 years, professor, clinical practicum supervisor, director of clinical training, internship advisor, and co-author on 5 publications. I truly appreciate all that I have learned from him and am excited to add "colleague" to list of relationships.

I would also like to offer a special thank you to the Geriatric Psychiatry Team at The Nathan S. Kline Institute for Psychiatric Research (NKI). I reflect fondly on my time as a fellow team member and am grateful for use of the MERI data, which made this dissertation possible.

Gratitude to my parents is also due for providing an upbringing that fostered a passion for helping others and endless intellectual curiosity.

Much has changed in the 5 years I have spent pursuing this degree, but the most rewarding and enduring of those changes were the births of my son, Yonah, and daughter, Tehilla, who have been a source of inspiration and motivation. And to my wife Rivka: Thank you for allowing me the opportunity to reach this milestone by providing

me with the emotional, physical, and yes, financial, support throughout these years. This achievement is as much yours as it is mine.

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Introduction

The two most common respiratory diseases are asthma and chronic obstructive pulmonary disease (COPD). Asthma is a relatively common chronic disease that affects over 8% of adults in the United states (Centers for Disease Control and Prevention, 2018). Common asthma symptoms include chest tightness, coughing or wheezing, and shortness of breath. A frequent physiological effect of asthma is thickening of the muscles comprising the airway, resulting in reduced airflow to the lungs. Certain conditions, such as stress, excessive activity, and infection, may subject individuals with asthma to hypoxemia, a low blood-oxygen level, which interferes with oxygen supply to vital organs, including the brain. Asthma attacks that increase the severity of asthma symptoms can create hypoxic conditions, resulting in potentially dangerous levels of oxygen deprivation. Chronic obstructive pulmonary disease (COPD), whose etiology is often attributed to smoking, or exposure to other pollutants, can be more severe than asthma, as it is chronic and progressive in nature. Diseases included under the umbrella of COPD are emphysema, a disease in which air is trapped in damaged parts of the lung preventing proper airflow, and chronic bronchitis, chronic inflammation of the channel that brings air to and from the lungs. Although COPD has a lower prevalence than asthma of just over 4% (Doney et al., 2014), both share common symptomatology, pathophysiology, and the potential for functional impairment due to oxygen deprivation. Other respiratory diseases, such as sleep apnea, a condition that manifests in abnormal breathing patterns, often with pauses that delay oxygen intake, and pulmonary fibrosis, a condition in which scar tissue on the lung restricts oxygen flow, also result in decreased oxygenation. This rationale is the general basis for scientific research investigating

cognitive functioning in people with respiratory diseases. Cerebral oxygenation is the fuel for brain functions, especially motor and higher-order processes.

The association between respiratory disease and cognitive functioning does not merely stem from a theoretical argument. Neuroimaging research has demonstrated that patients with asthma and COPD, the two most common respiratory illnesses, can yield structural changes in the brain that may influence execution of cognitive abilities, especially in hippocampal and gray matter areas, which are particularly sensitive to oxygen deprivation (Caldera-Alvarado et al., 2013; Dodd et al., 2012; Esser et al., 2016; Moss et al., 2005). Additionally, corticosteroid use is a common form of treatment for both asthma and COPD, which has been implicated in cognitive impairment by way of affecting the hippocampus and frontal lobe (Belanoff et al., 2001; Brown et al., 1999; Carlson et al., 2017). These areas are particularly noteworthy as they are associated with executive functions, learning, memory, spatial perception, language, and emotions (Leupoldt et al., 2011; Lezak et al., 2004). Related structural changes in the brain establish an even stronger rationale for investigating neuropsychological functioning in this population. It should be noted, however, that some have found that while use of corticosteroids may have a negative impact on executive functioning and memory, it has been associated with a positive effect on expressive language and some other functions (Bozek et al., 2010; Prado & Crowe, 2019).

A challenge in this line of research is identifying the relative impact of comorbid psychological and medical conditions in the relationship between respiratory disease and cognitive performance. There is an abundance of literature documenting a high

prevalence of depression and anxiety among patients with asthma or COPD (Briraatek et al., 2015; Del Giacco et al., 2016; Han, Forno, Marsland, Miller, & Celedón, 2016; Yohannes, Willgoss, Baldwin, & Connolly, 2010) and because anxiety and depression are known to negatively impact neuropsychological functioning even in the absence of asthma or COPD (Geda et al., 2014; Rock et al., 2014), it is important to ascertain whether respiratory disease affects functioning in a direct path, or whether these psychological comorbidities account for the effect. Asthma and COPD have also been shown to co-occur with numerous medical comorbid diseases, most commonly cardiovascular and metabolic diseases and especially in elderly populations (Soriano et al., 2005; Su et al., 2016; Tsai et al., 2012; Wardzyńska et al., 2015; Yáñez et al., 2014). Similarly, cardiovascular, cerebrovascular, and metabolic diseases, such as hypertension, congestive heart failure, stroke, and diabetes, to name a few, have also been associated with cognitive impairment, further complicating the process of evaluating their relative impact on cognitive functioning in the presence of asthma or COPD (McCrimmon et al., 2012; Waldstein & Elias, 2015).

Research to date on the relationship between respiratory disease and neuropsychological functioning is limited, especially with older adult populations (Irani et al., 2017; Tsai et al., 2012). However, numerous factors suggest that this older adult subset of the population deserves particular focus in the study of cognition among respiratory disease patients. Firstly, the above-mentioned comorbidities are more common in an older population, increasing the potential risk for cognitive impairment. Additionally, it is important to consider if and how cognitive processing among older patients with respiratory disease differs from normal cognitive aging among healthy older

adults (Irani et al., 2017). Some studies have also pointed to increased severity of asthma/COPD among the elderly, and an increased likelihood of consequential reduced cognitive functioning among older adults (Caldera-Alvarado et al., 2013; Dodd, 2015; Irani et al., 2017; Ray et al., 2015; Rusanen et al., 2013; Zein et al., 2015). One scientific approach suggests that asthma among older adults manifests in a manner phenotypically distinct from childhood asthma and that it is essentially classified as the same disease as COPD (Yáñez et al., 2014). Thus, the elderly asthma/COPD cohort becomes an important one to study in the context of both disease severity, as well as increased likelihood of psychological and medical comorbidities.

Research findings addressing the impact of respiratory disease (most commonly investigating asthma, COPD, or both) on neuropsychological functioning in the elderly are not only limited, but inconsistent. To summarize, some studies found minimal or no relationship between asthma/COPD and neuropsychological performance in the elderly (e.g., Caldera-Alvarado et al., 2013; Dodd, 2015; Moss et al., 2005; Salık et al., 2007), and others identified that asthma/COPD patients exhibited poorer cognitive performance than healthy counterparts (e.g., Crişan et al., 2014; Hung et al., 2009; Mourad et al., 2017; Torres-Sánchez et al., 2015). Some of these studies used a single, brief test of global cognition as a proxy for neuropsychological functioning rather than several scales that span multiple cognitive domains. Additionally, the impact of most of these studies is limited due to either small sample size, lack of a comparison group to the asthma or COPD groups, or a failure to account for the effects of relevant comorbidities. For example, cardiovascular disease has long been linked with poor cognitive outcomes, attributed to some of the risk factors that accompany the disease, subclinical strokes, and

more recently, structural brain changes due to cardiovascular disease (Johansen et al., 2020; Leritz et al., 2011). Specific deficits have been noted with higher-order functions, such as cognitive flexibility and processing speed, as assessed with the Digit Symbol Test (Hajjar et al., 2011). Others also found that cardiac health was associated with some higher-order cognitive processes, such as psychomotor tasks, executive functioning, and global cognition, but also that it was seldom associated with verbal processes. (Crichton et al., 2014). Additionally, psychological comorbidities like depression and anxiety have also been associated with poorer cognitive performance in the elderly, especially in the domains of processing speed, memory, attention, and executive control (Beaudreau & O'Hara, 2009; Geda et al., 2014; Rock et al., 2014; Shimada et al., 2014). The interactions of comorbidities in their relationships with each other and with cognitive functioning increases the complexity of investigating relative effects of each factor. Research evaluating the link between respiratory disease and cognitive functioning must properly execute sound methodological strategy as well as account for the possible effects of these comorbidities in order to draw translatable conclusions.

In a preliminary study, the current author investigated group differences in neuropsychological functioning between asthma, COPD, and comparison groups of older adults (Gordon, 2019). Using a quasi-experimental design, with a large sample size and numerous neuropsychological measures spanning various cognitive domains, the research did not reveal meaningful group differences in any of the domains assessed (executive functioning, complex attention, verbal memory, language, visual construction, and psychomotor functioning). However, despite the absence of statistically meaningful group differences, an observable trend suggested that COPD patients may have

performed more poorly than controls on tasks in which the cognitive complexity or psychomotor demands increased from trial to trial in the task (e.g., when using non-dominant hand versus the dominant hand). This research, however, did not account for the psychological and medical comorbidities known to influence cognitive functioning that may have impacted the results. Additionally, unlike some of the earlier work in this area, physiological measures of respiratory disease function were not reviewed in the context of neuropsychological performance.

The aims of the current study were: 1) to build upon previous research on the impact of respiratory disease on neuropsychological functioning in older adults by evaluating the role of key psychological and medical comorbidities most likely to impact functioning (i.e., cardiovascular diseases and depression); 2) To examine the impact of a broad group of respiratory diseases with similar pathophysiology (e.g., including sleep apnea, pulmonary fibrosis) on cognition and to further explore differences between asthma and COPD subgroups in comparison; 3) To explore patterns of physiological differences between groups and their potential relationship with cognitive performance using measures of blood pressure and oxygen saturation levels. In light of research suggesting that respiratory illness is more likely to affect more cognitively demanding aspects of neuropsychological functioning, especially tasks requiring cognitive flexibility and psychomotor functions (e.g., Irani et al., 2017; Moss et al., 2005; Rajabi, Keshavarz, Dehghani, Keshavarz, & AliMoradi, 2018), focus was devoted to performance on such tests.

Hypotheses

1) It was expected that ratings for both psychological disorders (i.e., depression and anxiety) would correlate negatively with neuropsychological measures, indicating that more severe depression and anxiety would reflect poorer cognition.
2) All neuropsychological test measures were expected to correlate with one another, allowing for examination of a global cognition score in addition to more specific domains.
3) It was expected that both cardiovascular disease and depression would relate to performance on global cognition, psychomotor functioning, and verbal ability, such that those with self-reported cardiovascular disease and higher depression scores would perform more poorly in these domains than those in a reference group. Literature supports a hypothesis that cardiovascular disease would have the greatest impact in the domain of psychomotor functioning.
4) It was also expected that after accounting for the effects of cardiovascular disease and depression, that respiratory disease would be related to poorer performance in all three domains. It was further anticipated that COPD would be more strongly implicated over asthma in poorer performance due to COPD's more severe symptomatology.
5) Lower oxygen and higher blood pressure levels were expected to correlate with poorer performance in all cognitive domains.

Method

The data for this study was collected from participants of the Memory Education and Research Initiative (MERI), an ongoing clinical research program that measures a wide range of medical, behavioral, cognitive, and demographic data (Reichert et al., 2015). Participants are typically referred to the MERI for neuropsychological testing secondary to subjective memory complaints or concerns regarding a family history of dementia. Many, if not most of the MERI participants, however, are found not to be cognitively impaired from a clinical standpoint and comprise most of the research subjects included in this study. More detailed information regarding the participant pool has been previously published in a book chapter describing the MERI model (Reichert et al., 2015). Participants under the age of 60 years were excluded from this study consistent with previous studies of older adult cohorts using similar age cutoffs. In preliminary research (Gordon, 2019), subjects considered to be cognitively impaired as determined by Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) scores below 24, a conventional cutoff for this measure (Lezak et al., 2004), were excluded. The current research aimed to enhance methodology by removing the MMSE cutoff criterion, recognizing that physical disease may facilitate cognitive impairment and by excluding those with clinical impairment, the overall data may have been misrepresented.

Participants

After excluding participants below 60 years old and who did not complete any neuropsychological test, a total of 969 participants were included, comprising groups of those without cardiovascular or respiratory disease, those with both disease types, those

with only cardiovascular disease, the largest subgroup, and those with only respiratory disease. See Figure 2 for a visual representation of these groups. Participants had mean age of 74 years, were mostly female (60%), and attained 15 years of education, on average. Not all participants completed the full protocol of cognitive tests due to either physical or cognitive handicap, refusal, or because tests were only introduced to the study protocol at a later time

Procedures

Study procedures have been approved by the institutional review boards of the Nathan S. Kline Institute for Psychiatric Research and St. John's University. A detailed account of operations of the MERI can be found in the MERI book chapter (Reichert et al., 2015). Informed consent was obtained from all participants at initial contact. The components of the MERI that contributed to the current research include a detailed medical history, a brief medical exam, and a comprehensive neuropsychological battery. All medical data, including diagnoses of respiratory and cardiovascular disease and other medical history, as well as demographic information, were obtained by medical professionals via participant self-report during the intake process. Physiological measures, including blood-oxygen, blood pressure, and pulse, among other vital signs, were also measured at this time. Following intake, the neuropsychological test battery was administered by a trained psychometrician in a quiet room devoted to testing procedures. Following medical intake and neuropsychological testing, all MERI participants participated in a clinical interview with a geriatric psychiatrist.

Data collected as part of the MERI were entered, stored, and cross-checked with paper files in a secure database. After all MERI visits, brief reports were compiled and reviewed in consultation with a clinical neuropsychologist and geriatric psychiatrist and results were mailed to participants.

Neuropsychological Measures

Descriptions of all neuropsychological tests administered as part of the MERI program are contained in the MERI book chapter (Reichert et al., 2015). Brief descriptions of the tests examined as part of the current study are provided below.

Mini Mental State Examination (MMSE; Folstein et al., 1975). Used as a measure of global cognitive functioning and a cutoff criterion (scores < 24) for cognitive impairment. The MMSE is a brief assessment that screens for potential problems in the areas of orientation, registration, attention and calculation, recall, and language. The test consists of both verbal and paper-and-pencil responses. The maximum score, indicating higher performance, is 30 points.

Rey Auditory Verbal Learning Test (AVLT; Rey, 1958). Used as a measure of verbal memory, the AVLT encompasses five learning trials of a 15-word list, yielding a total recall score with a maximum of 75 words, an immediate test of uncued recall of words after an "interference" word list is presented, a delayed test of uncued recall of the original words after a 20-25 min delay, and a recognition task involving cued, multiple-choice recall of the original word list. Scores represent the number of words accurately recalled.

Boston Naming Test (abridged; Kaplan et al., 1983). An abridged version of a 60-item confrontation naming measure requires respondents to name what they see in 30 drawings, which range from familiar objects to less familiar ones. If a participant fails to produce a response, a semantic cue is provided, followed by a phonetic cue if the respondent has difficulty naming even with a semantic cue. This test is used to assess language ability, with scores representing the number of items correctly named out of 30.

Digit Symbol Substitution (Wechsler, 1939). A timed coding test in which participants are to use a key with paired numbers and symbols to complete a grid, which has numbers in the top portion and empty boxes in the lower portion, by filling in the corresponding symbols into the empty boxes. This test is used to measure both complex attention and processing speed, as well as serve as a proxy for executive functioning. Scores represent the number of symbols accurately transcribed.

Grooved Pegboard (Lafayette Instruments; Model 32025). In this timed task, participants are asked to use metal pegs with one notched side to fill an arrangement of five rows with five slots each. Slots are oriented in different directions, requiring participants to maneuver pegs to fit accordingly. Scores on this test indicate the amount of time (in seconds) needed to complete the task. This test has separate trials for dominant and non-dominant hands. Grooved Pegboard is a more complex task of psychomotor functioning and is also a correlate of general cognitive ability. Because higher scores indicate poorer performance, scores were reversed for statistical analyses.

Trail Making Test A (TMTA) & B (TMTB; Reitan, 1992). This test has two parts. Part A has participants draw lines sequentially connecting a series of circles with

numbers. Part A tests for attention and visual tracking, but also letter sequencing. The more complex Part B requires drawing lines sequentially, but this time alternating between both numbers and letters. Part B measures complex attention and the executive function of cognitive flexibility. Scores on this test indicate the amount of time (in seconds) needed to complete the task. Because higher scores indicate poorer performance, scores were reversed for statistical analyses.

Verbal Fluency (FAS; Spreen & Benton, 1977) and Category Fluency (Animals; Moms et al., 1989). In Verbal Fluency (FAS), also known as the Controlled Oral Word Association Test (COWAT), participants are asked in three different trials to produce as many words as they can in 1 min that begin with the letters F, A, and S, respectively. Credit is not awarded for proper nouns, numbers, and the same word with a different suffix. In Category Fluency (Animals), participants are asked to name as many animals as they can in 1 min. These tests are associated with both executive functioning and the verbal fluency aspect of language. Scores on these tests indicate the amount of valid words produced in the allotted 1 min.

Vocabulary. This test asks participants for definitions of words, ranging in difficulty level. It is an assessment of language attainment. Definitions are scored according to precision and quality, with higher scores indicating better performance.

Although several of these tests may represent multiple cognitive domains, scores were aggregated to assess three core domains: global cognition, psychomotor functioning, and verbal ability. Categorization of domains was based largely on theory and precedents. Global cognition is an aggregate of scores for all neuropsychological

tests (excluding MMSE), representing a generalized level of overall cognitive performance in a more comprehensive manner than brief screeners like the MMSE that only contain one or several individual test items to represent domains. The psychomotor/executive functioning domain is an aggregate of scores of tests of higher-order processing and psychomotor functioning (e.g., cognitive flexibility, processing speed, manual dexterity) and includes the following tests: Digit Symbol, Trail Making Test B, and Grooved Pegboard. Verbal ability is an aggregate of test scores that have a verbal or language component (e.g.., verbal memory and learning, verbal fluency, confrontation naming, letter sequencing) and includes the following tests: AVLT total recall, Verbal Fluency, Category Fluency, Trail Making Test A, Vocabulary, and Boston Naming. A visual depiction of domain aggregate scores can be found in Figure 1.

Psychological Measures

Depression. Multiple valid and reliable measures of depression were administered as part of the MERI program, including the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960), Beck Depression Inventory (BDI; Beck et al., 1996), Profile of Mood States (POMS; McNair et al., 1971), which has a Depression subscale, and the Geriatric Depression Scale (GDS; Yesavage et al., 1982). Aggregate scores of depression scales were used for participants who completed multiple scales.

Anxiety. Scales of anxiety were also administered as part of the MERI, including the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959), Beck Anxiety Inventory (BAI; Beck et al., 1988), and Profile of Mood States (POMS; McNair et al., 1971), which

has a Tension-Anxiety subscale. Anxiety scale scores were also aggregated for participants who completed multiple scales.

Medical Diseases

Cardiovascular. Cardiovascular disease includes a wide range of heart-related conditions and illnesses. Some of the most common ones endorsed by participants include: hypertension, history of heart attack, atrial fibrillation, stents or pacemakers, arrythmia, coronary artery disease, and congestive heart failure. Cardiovascular disease was measured by patient self-report during intake.

Respiratory. Respiratory disease in the current study includes self-reported history of the following: asthma, COPD, sleep apnea, and pulmonary fibrosis. Respiratory disease was measured by patient self-report during intake.

Data Analytic Strategy

Group differences among demographic variables were tested with either Chi-square tests or independent samples t-tests. Zero-order correlations were used to assess for relationships between psychological, neuropsychological, and medical disease variables to identify variables of interest, test for multicollinearity, and justify aggregation of related scales. To test for relationships between independent variables and dependent variables, hierarchical multiple regressions were conducted for all three cognitive domains in three variations to allow for examination of groups that include all respiratory diseases, asthma alone, and COPD alone. On occasion, test scores presented

with extreme values. In these instances, winsorization was used to rectify the outlying data. All analyses were conducted using IBM SPSS Statistics Version 25.

Results

For possible differences between the respiratory and reference groups on demographic variables that relate to cognition, Chi-square tests and independent samples t-tests were conducted to evaluate group differences in gender, age, and years of formal education. The tests revealed no meaningful differences between the groups with respect to gender (p = .88), age (p = .23*)* and years of education (p = .42*)*. Therefore, these demographic variables were omitted from further analyses. Additionally, aggregate anxiety scores did not demonstrate a meaningful relationship with either cardiovascular or respiratory disease and did not account for group differences (p > .05). It was, therefore, not implicated as a variable that suppressed the relationship between respiratory disease and cognition. As a result, anxiety was omitted from the primary analyses (i.e., regression analyses). Means and standard deviations for neuropsychological tests in raw score form and mean z-scores for aggregate depression and anxiety are provided in Table 1 for the whole sample, the respiratory disease group, and the cardiovascular disease group. All aggregate scores (i.e., depression, anxiety, cognitive domains) were calculated by converting raw scores of individual tests to z-scores, then adding scores together and taking the mean for each participant.

Although anxiety did not correlate with either disease type, it did correlate meaningfully with depression (r = .83, p < .001) and weakly, but meaningfully, with the cognitive domains of global cognition (r = -.11, p < .001), psychomotor functioning (r = -.13, p < .001), and verbal ability (r = -.09, p = .007), suggesting that higher levels of anxiety correspond to higher levels of depression and poorer performance in all cognitive

domains. Additionally, all test scores correlated meaningfully with one another at the $p <$ .001 level. This finding justifies the examination of a global cognition score that takes broader cognitive performance into account. This also served as a basis to create aggregate scores for the cognitive domains of psychomotor functioning and verbal ability. Similarly, all the depression subscales that comprise the aggregate depression score correlated with one another.

Hierarchical regression analyses were performed in order to determine the impact of three groups of participants with respiratory disease (all, asthma, COPD) on global cognition, after controlling for the comorbidities of cardiovascular disease and depression. Preliminary analyses were conducted to ensure no violation of regression assumptions. Cardiovascular disease and depression were entered in the first step and respiratory disease group in the second step. As shown in Table 3, comorbidities (i.e., cardiovascular disease, depression) explained 4% of the variance in global cognition scores. Diagnosis of cardiovascular disease and higher depression scores were associated with poorer performance on overall cognition, β = -.07, p = .028 and β = -.18, p <.001, respectively. After entering respiratory disease at Step 2, the total variance explained by the model was 5%, $F(3, 958) = 14.82$, $p < .001$. Respiratory disease accounted for only an additional 1% of variance in the final model, β = .10, p = .002. Although small in effect, in the final model, all three variables, cardiovascular disease, depression, and respiratory disease, were statistically meaningful. Individual Beta values, standard errors, *p*-values, and change in R-squared can be found in Table 3. It is important to note that, contrary to hypothesis, those with respiratory disease were found to indicate better global cognitive performance.

To account for possible differences between groups of the most common respiratory diseases, asthma and COPD, hierarchical regressions were rerun two more times, entering asthma and COPD, respectively, into Step 2. Results can be found in Table 3. For both regression analyses, comorbidities (i.e., cardiovascular disease, depression) again explained 4% of the variance in global cognition scores. Diagnosis of cardiovascular disease and higher depression scores were associated with poorer performance on overall cognition. The first model revealed that cardiovascular disease and depression predicted global cognition scores for both asthma, $F(2, 888) = 17.88$, $p < .001$, and COPD, $F(2, 868) = 18.90$, $p < .001$, but after entering respiratory groups in Step 2, no additional variance was explained by the model and no meaningful effect was found for asthma ($p = .131$) or COPD ($p = .106$) on global cognition.

Hierarchical regression analyses were also conducted to determine the relative impact of cardiovascular disease, depression, and respiratory group on psychomotor functioning. As with earlier analyses, cardiovascular disease and depression were entered in the first step and respiratory disease group in the second step. As shown in Table 4, comorbidities (i.e., cardiovascular disease, depression) explained 5% of the variance in psychomotor functioning scores. Diagnosis of cardiovascular disease and higher depression scores were associated with poorer performance on psychomotor tasks, $\beta = -.12$, $p < .001$ and $\beta = -.18$, $p < .001$, respectively. This model revealed predictive power of these comorbidities on psychomotor functioning, $F(2, 924) = 18.18$, $p < .001$. Step 1 remained statistically meaningful in explaining variance in psychomotor functioning in regression analyses examining asthma (4%), $F(2, 854) = 21.94$, $p < .001$, and COPD (5%), $F(2, 833) = 21.81$, $p < .001$, independently. However, in all three

regressions, Step 2, that is, including respiratory group in the predictive model to explain psychomotor scores, did not explain additional variance in scores, suggesting no relationship between respiratory disease and psychomotor functioning when controlling for the effects of cardiovascular disease and depression.

One final set of hierarchical regression analyses were performed in order to determine the impact of three groups of participants with respiratory disease (all, asthma, COPD) on verbal ability, after controlling for the comorbidities of cardiovascular disease and depression. Cardiovascular disease and depression were entered in the first step and respiratory disease group in the second step. As shown in Table 5, this model differed from regressions examining overall cognition and psychomotor ability in that comorbidities (i.e., cardiovascular disease, depression) only explained 2% of the variance in verbal ability scores and that even this effect was carried by depression, $\beta = -.14$, $p < .001$; $F(2, 956) = 11.16$, $p < .001$, and cardiovascular disease did not appear to share a meaningful relationship with verbal ability. After entering respiratory disease at step 2, the total variance explained by the model was 3%, $F(3, 955) = 11.88$, $p < .001$. All respiratory disease accounted for only an additional 1% of variance in the final model, $\beta = .11$, $p < .001$, revealing that respiratory disease diagnosis was related to higher verbal performance. In step 2, depression ($p < .001$) and respiratory disease ($p < .001$) meaningfully predicted verbal ability, whereas cardiovascular disease showed a possible trend ($p = .059$). As described, presence of comorbidities was related to poorer performance and presence of respiratory disease was related to better performance.

To further explore the unanticipated finding of respiratory disease predicting better verbal ability, hierarchical regressions were once again conducted two additional times, entering asthma and COPD, respectively, into Step 2. Results can be found in Table 5. For both regression analyses, comorbidities explained 3% of the variance in verbal ability, again carried primarily by depression, such that higher depression scores indicated poorer verbal ability in step 1 of regressions that examined asthma, $F(2, 884) = 11.53$, $p < .001$, and COPD, $F(2, 864) = 11.51$, $p < .001$. However, in examining the additive predictive effect of COPD on verbal ability, it was found that, although the additional variance explained by this model was minimal (< 1%), COPD was meaningfully related to better verbal ability. Unlike with COPD, asthma offered no additional predictive effect on verbal ability.

To explore further, additional multiple regressions were executed testing for moderation. All nine multiple regressions previously conducted (predicting scores on the three cognitive domains for three groups of respiratory disease) were re-run two more times, entering interaction terms for respiratory disease X cardiovascular disease and respiratory disease X depression, respectively into Step 3 of the regression analyses. Results of analyses revealed that interactions of the respiratory disease groups with cardiovascular disease and depression did not add any meaningful incremental prediction of cognitive scores for any of the domains (ps > .05).

Means and standard deviations for physiological variables are reported in Table 6, along with clinical norms for an older adult population compiled from medical sources (Beasley et al., 2017; McCance & Huether, 2018; Whelton et al., 2018). With the

exception of systolic blood pressure, physiological measures (diastolic blood pressure, respiration, and oxygen saturation) were found to be in the normal range for all groups. Systolic blood pressure was found to be in the range consistent with Stage 2 hypertension, not unexpected given that about 70% of the total sample reported diagnosed cardiovascular disease. Additionally, no meaningful differences between the respiratory and cardiovascular groups and their reference groups were found, except that those with self-reported cardiovascular disease had higher systolic blood pressure than a reference group without cardiovascular disease, $t(957) = 1.84$, $p = .02$, an expected and small effect. Correlations were run to explore relationships between physiological measures and cognitive domains, also revealing no meaningful relationships between any of the physiological measures and the three cognitive domains.

Discussion

The primary goals of the current study were to examine the relationship between a group of common respiratory diseases (asthma, COPD, sleep apnea, and pulmonary fibrosis) and global cognition, psychomotor functioning, and verbal ability in older adults, while also evaluating the impact of cardiovascular disease, depression, and anxiety in this relationship. It was hypothesized that cardiovascular disease and depression would both correlate with poorer cognitive functioning in all domains and that, after controlling for cardiovascular disease and depression, a relationship between respiratory disease and poorer functioning would emerge, with COPD demonstrating a stronger effect as compared to asthma.

Regarding predictions about cardiovascular disease, the research largely supported the hypotheses. Cardiovascular disease was related to poorer performance on global cognition, which, when further broken down into the domains of psychomotor functioning and verbal ability, appeared to limit the effect to psychomotor functioning. Although a stronger effect was correctly predicted in the psychomotor domain, it was also expected that the effect would translate to verbal ability, which was not the case when verbal ability was examined apart from global cognition. As an aside, this may be consistent with the oft-cited distinction between crystallized and fluid intelligence, that crystallized intelligence can remain intact even in cognitively compromised populations, whereas fluid intelligence may decline sooner in compromised populations or in tandem with normal aging (Horn & Cattell, 1967). With regard to depression, hypotheses were fully supported. Depression predicted poorer functioning in global cognition, as well as when broken down into the domains of psychomotor and verbal ability. The effects of

cardiovascular disease and depression remained essentially unchanged across analyses of all included respiratory diseases, asthma alone, and COPD alone. Although the combined impact of cardiovascular disease and depression was meaningful, the effect was minimal. Only 2-3% of the variability in verbal ability scores and 4-5% in psychomotor scores was explained by cardiovascular disease and depression.

Although when controlling for the noted effects of cardiovascular disease and depression, respiratory disease was found to meaningfully predict global cognition scores, it predicted better, not poorer, performance, contrary to hypothesis. This effect was also small, explaining only an additional 1% of variability in scores. Additionally, when examining this effect comparing asthma and COPD separately, neither one produced a significant effect on its own. Only the all-inclusive respiratory group exhibited the counterintuitive result. Further investigation revealed that with respect to psychomotor functioning, respiratory disease offered no statistical predictive quality on top of cardiovascular disease and depression. However, respiratory disease did add predictive quality over the comorbidities in the domain of verbal ability, possibly accounting for the effect seen in global cognition (which is comprised of verbal ability and psychomotor domains together). Furthermore, when comparing asthma to COPD in prediction of verbal ability scores, asthma alone did not appear to have an effect, whereas the COPD group seemed to account for the minimal effect predicting better verbal ability.

In summary, the only truly notable impact of respiratory disease on cognition was in the domain of verbal ability and the effect was a beneficial one, and more likely to be associated with COPD than asthma. This effect is counterintuitive, not only because the

direction of the relationship runs counter to previous research (e.g., Caldera-Alvarado et al., 2013; Dodd, 2015; Moss et al., 2005; Salık et al., 2007) and theoretical expectations, but especially because COPD, the more severe of the two types of respiratory disease, was the one that appears to account for the positive effect on verbal ability. Although it is possible to dismiss this finding because the statistical significance is borderline, the effect is minimal, and one could easily conclude that the current study is consistent with the research that respiratory disease in the elderly does not have a detectable impact on cognitive functioning, there may be a possible explanation for this effect. As noted earlier, some researchers have found that corticosteroid use can actually enhance some cognitive abilities, among them expressive language (Bozek et al., 2010; Prado & Crowe, 2019). Due to the severe nature of COPD relative to asthma, corticosteroid use may be more frequent and perhaps this could explain the presence of a beneficial effect only for the COPD group and only for verbal ability in contrast to psychomotor functioning. Nonetheless, this is speculative as no data for medications or disease management were included in this study. Whatever the reason, these findings seem to indicate contrary to the approach of Yáñez et al. (2014) that COPD and asthma are essentially the same disease in the elderly, as differences were observed in the current research when contrasting asthma and COPD subgroups. It could be suggested that the disease types are similar with respect to their pathophysiology, but their clinical presentations and severity appear to remain different.

Regarding secondary aims/hypotheses, as expected, both anxiety and depression were associated with poorer cognition, globally and within both the psychomotor and verbal domains. Additionally, all individual cognitive tests that compromised the

domains correlated with another, as expected, allowing for creation of the aggregate domain scores, but also affirming data integrity in the process.

An additional aim of this research was to explore the relationship between physiological measures known to correlate with heart and respiratory disease and to examine their impact on cognition. A study of the whole sample, as well as isolating the cardiovascular and respiratory groups, revealed that on average, physiological measures were in the normal range for diastolic blood pressure, oxygen saturation, and respiration (breaths per minute). The exception, systolic blood pressure, was found to have a mean on the cusp of hypertensive disease, which is consistent with a sample whose majority has been diagnosed with cardiovascular disease/hypertension. Nonetheless, none of these measures appeared to relate to the cognitive domains in a meaningful way. Also, aside from those with cardiovascular disease showing higher systolic blood pressure than a reference group without it, no other differences on these measures were found between those with and without cardiovascular disease and with and without respiratory disease. It is likely to infer from this that, although these groups of people had self-reported diagnoses of disease, diseases were either well-controlled by medical treatment or the severity of disease was mild, thus reflecting generally normal levels of physical disease indicators. This may also lend understanding as to why, by and large, meaningful relationships did not emerge between respiratory disease and neuropsychological functioning and why the effect size was smaller than anticipated, even for the associations between cardiovascular disease and depression on cognition. Perhaps more meaningful associations may have been observed in a sample of patients with greater disease severity.

Another point to consider regarding the failure to identify the expected negative relationship between respiratory disease and cognitive performance is that some have observed that asthma is underdiagnosed in the elderly (Banerjee et al., 1987; Stupka & deShazo, 2009). If this position is considered, it is possible the reference group utilized as a control for respiratory disease, a group of participants that was assumed to be cleared from diagnoses of respiratory diseases, may have, in fact, included those with undetected asthma, thereby skewing the results.

Limitations, Challenges, and Future Directions

Aside from those already alluded to, a number of limitations exist that may have impacted the extent of the findings or prevent generalization to clinical settings. Firstly, and perhaps most importantly, data on disease severity and treatment regimens were not obtained as part of this research. Data on reported severity may have been informative with respect to interpreting results and would have likely provided more context for the physiological data obtained. Additionally, accounting for the effects of medications, such as corticosteroids, may have provided more insight into results, as well. Another limitation may be the bias resulting from the "presenting problems" of the participants. As noted, MERI participants presented for neuropsychological testing primarily due to subjective memory or other cognitive complaints or out of concern due to aging and a family history of dementia or Alzheimer's disease. Although medical history was examined peripherally, the focus of the parent research was not to validate the diagnoses of respiratory or cardiovascular disease nor to recruit from medically unstable populations. As mentioned, it is possible that recruitment of participants from pulmonary

or cardiovascular specialty clinics may have been more appropriate for this type of research.

Another methodological downside using the MERI data for the current project is that neuropsychological test selection was intended to be sensitive to more basic cognitive changes typically associated with dementia and Alzheimer's disease. Perhaps the impact of respiratory disease on cognition via cerebral oxygen deprivation may be more subtle and require more sensitive tests or comprehensive tests of higher-order functioning (e.g., Delis-Kaplan Executive Function System [DKEFS; Delis et al., 2012]). This is compounded by the fact that in an older adult population, the effects of normal cognitive aging may also be at play. Additionally, a challenge in all neuropsychological assessment is that often, an individual test may correlate with or assess multiple domains, complicating the interpretation of findings. For example, the Category Fluency test in the current study is conventionally used as a measure of verbal ability but is also widely used as a measure of executive functioning, possibly confounding the results. A research program focused more narrowly on the effects of respiratory disease may take these considerations into account.

Finally, the current study only evaluated data at a single timepoint. Comparison of baseline functioning with performance at future visits, along with physiological measures obtained on multiple occasions, may provide a clearer picture of the clinical implications of medical disease on cognition.

Clinical Implications and Applications

There are numerous clinical implications of the current study. The relatively little the scientific community knows about how respiratory disease impacts neuropsychological functioning, let alone, in conjunction with comorbid conditions also known to impact functioning, can now benefit from expanded knowledge. Although results may be limited by the factors outlined above, in the current investigation the following basic pattern emerges: 1) depression relates to poorer cognition, globally, and within the individual domains of verbal ability and psychomotor functioning 2) cardiovascular disease relates to poorer functioning most significantly in the domain of psychomotor functioning 3) respiratory disease does not appear to explain cognitive performance, with the possible exception of COPD relating to enhanced performance in verbal ability. These findings can prepare medical practitioners to anticipate, as well as appropriately screen for neuropsychological impairment in the related domains. Monitoring and screening could then inform treatment planning and development of compensatory cognitive strategies, when indicated. For example, a patient who presents to a medical professional and is diagnosed with COPD may also be screened for depression and cardiovascular disease. Depending on the results, practitioners may want to refer for additional screening for deficits in either verbal or psychomotor domains. A patient with heart disease may be educated to apply extra caution when engaging in potentially hazardous motor-related tasks or be guided to maximize on the likelihood of preserved verbal and language functions in personal or professional settings.

Recently, the global COVID-19 pandemic has resulted in many infected patients presenting with oxygen deprivation secondary to hypoxic conditions not unlike those seen in asthma or COPD (Rahman et al., 2021). It has yet to be seen how COVID-19 may relate to cognition, especially longitudinally, but future research utilizing the theoretical framework outlined in this study may prove useful.

Tables

Table 1

Means and Standard Deviations of Neuropsychological Test Raw Scores and Z-scores for Aggregate Depression and Anxiety by Group

	All Participants *n* = 969	Respiratory Disease *n* = 196	Cardiovascular Disease *n* = 678
Neuropsychological Tests	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
MMSE	26.60 (4.80)	27.44 (3.76)	26.57 (4.72)
AVLT-Total Recall	36.16 (14.03)	38.40 (12.34)	35.34 (13.67)
Verbal Fluency (FAS)	37.00 (16.79)	40.22 (17.23)	36.39 (17.26)
Category Fluency	14.63 (6.84)	16.37 (7.07)	14.37 (6.95)
Boston Naming	22.89 (6.50)	23.87 (5.92)	22.73 (6.45)
Vocabulary	11.05 (3.00)	11.41 (2.78)	11.06 (3.00)
Trail Making Test A	50.85 (30.04)	47.58 (26.34)	52.53 (31.12)
Trail Making Test B	115.91 (65.44)	112.59 (63.89)	119.87 (67.20)
Digit Symbol	38.72 (14.38)	39.08 (14.63)	37.42 (14.14)
Grooved Pegboard (DH)	110.52 (44.17)	108.98 (38.93)	112.68 (43.52)
Grooved Pegboard (non DH)	121.16 (47.88)	123.19 (44.99)	124.07 (47.26)
Aggregate Z-scores			
Depression	-.01 (.86)	.14 (.91)	.01 (.89)
Anxiety	-.02 (.84)	.09 (.90)	.00 (.85)

Note. For the following tests, higher scores represent poorer performance (i.e., time, in seconds, to complete the task): Grooved Pegboard, TMTA, TMTB. For all other tests, higher scores indicate better performance. For depression and anxiety, higher z-scores indicate greater disease severity.

Table 2
Correlation Coefficients of Neuropsychological Test Scores

	1	2	3	4	5	6	7	8	9	10
1. AVLT-Total	1									
2. VF (FAS)	.56*	1								
3. VF (Animals)	.66*	.65*	1							
4. Boston Naming	.58*	.55*	.70*	1						
5. Vocabulary	.52*	.60*	.59*	.65*	1					
6. TMT-A	.49*	.45*	.56*	.52*	.39*	1				
7. TMT-B	.47*	.46*	.52*	.45*	.38*	.67*	1			
8. Digit Symbol	.63*	.59*	.67*	.61*	.49*	.72*	.66*	1		
9. GP (DH)	.40*	.27*	.40*	.37*	.31*	.48*	.43*	.50*	1	
10. GP (non DH)	.34*	.28*	.37*	.32*	.24*	.43*	.46*	.47*	.75*	1

Note. * $p < .001$; AVLT = Auditory Verbal Learning Test; VF = Verbal Fluency; TMT = Trail Making Test; GP = Grooved Pegboard); DH = dominant hand

Table 3

Hierarchical Linear Regression Predicting Global Cognition from Cardiovascular Disease, Depression, and Respiratory Disease Groups

	All Respiratory				Asthma				COPD			
Variable	***β***	***SE***	***p***	**ΔR^2**	***β***	***SE***	***p***	**ΔR^2**	***β***	***SE***	***p***	**ΔR^2**
Step 1				.04*				.04*				.04*
Cardiovascular	-.07	.06	.028		-.07	.06	.038		-.07	.06	.028	
Depression	-.18	.03	<.001		-.18	.03	<.001		-.19	.03	<.001	
Step 2:				.01*				<.01				<.01
Cardiovascular	-.08	.06	.016		-.07	.06	.036		-.08	.06	.023	
Depression	-.18	.03	<.001		-.18	.03	<.001		-.19	.03	<.001	
Respiratory Group	.10	.07	.002		.05	.09	.131		.05	.10	.106	

Note. *p≤.01

Table 4

Hierarchical Linear Regression Predicting Psychomotor Functioning from Cardiovascular Disease, Depression, and Respiratory Disease Groups

	All Respiratory				Asthma				COPD			
Variable	***β***	***SE***	***p***	**ΔR^2**	***β***	***SE***	***p***	**ΔR^2**	***β***	***SE***	***p***	**ΔR^2**
Step 1				.05*				.04*				.05*
Cardiovascular	-.12	.06	<.001		-.13	.07	<.001		-.12	.07	<.001	
Depression	-.18	.03	<.001		-.18	.04	<.001		-.18	.04	<.001	
Step 2:				<.01				<.01				<.01
Cardiovascular	-.12	.06	<.001		-.13	.07	<.001		-.12	.07	<.001	
Depression	-.18	.03	<.001		-.18	.04	<.001		-.18	.04	<.001	
Respiratory Group	.04	.07	.191		.02	.10	.481		.02	.11	.638	

Note. *p≤.01

Table 5

Hierarchical Linear Regression Predicting Verbal Ability from Cardiovascular Disease, Depression, and Respiratory Disease Groups

	All Respiratory				Asthma				COPD			
Variable	***β***	***SE***	***p***	**ΔR^2**	***β***	***SE***	***p***	**ΔR^2**	***β***	***SE***	***p***	**ΔR^2**
Step 1				.02*				.03*				.03*
Cardiovascular	-.05	.07	.098		-.05	.07	.146		-.06	.07	.088	
Depression	-.14	.04	<.001		-.15	.04	<.001		-.15	.04	<.001	
Step 2:				.01*				<.01				<.01**
Cardiovascular	-.06	.07	.059		-.05	.07	.138		-.06	.07	.073	
Depression	-.15	.04	<.001		-.15	.04	<.001		-.15	.04	<.001	
Respiratory Group	.11	.08	<.001		.06	.11	.093		.07	.12	.053	

Note. *p≤.01; ** p≤.05

Table 6

Means, Standard Deviations, and Clinical Norms of Physiological Variables

Physiological Indicators	All Participants $n = 959$ *M* (*SD*)	Respiratory Disease $n = 195$ *M* (*SD*)	Cardiovascular Disease $n = 671$ *M* (*SD*)	Clinical Norms for Older Adults
Systolic BP (sitting)	139.59 (19.39)	137.31 (18.38)	140.56 (19.40)	< 130
Diastolic BP (sitting)	75.86 (10.44)	75.87 (10.44)	75.66 (10.57)	< 80
Oxygen Saturation (%)	97.84 (1.75)	97.54 (1.67)	97.69 (1.84)	92 - 100
Respiration (BPM)	17.71 (2.28)	17.90 (2.08)	17.70 (2.38)	12 - 20

Figures

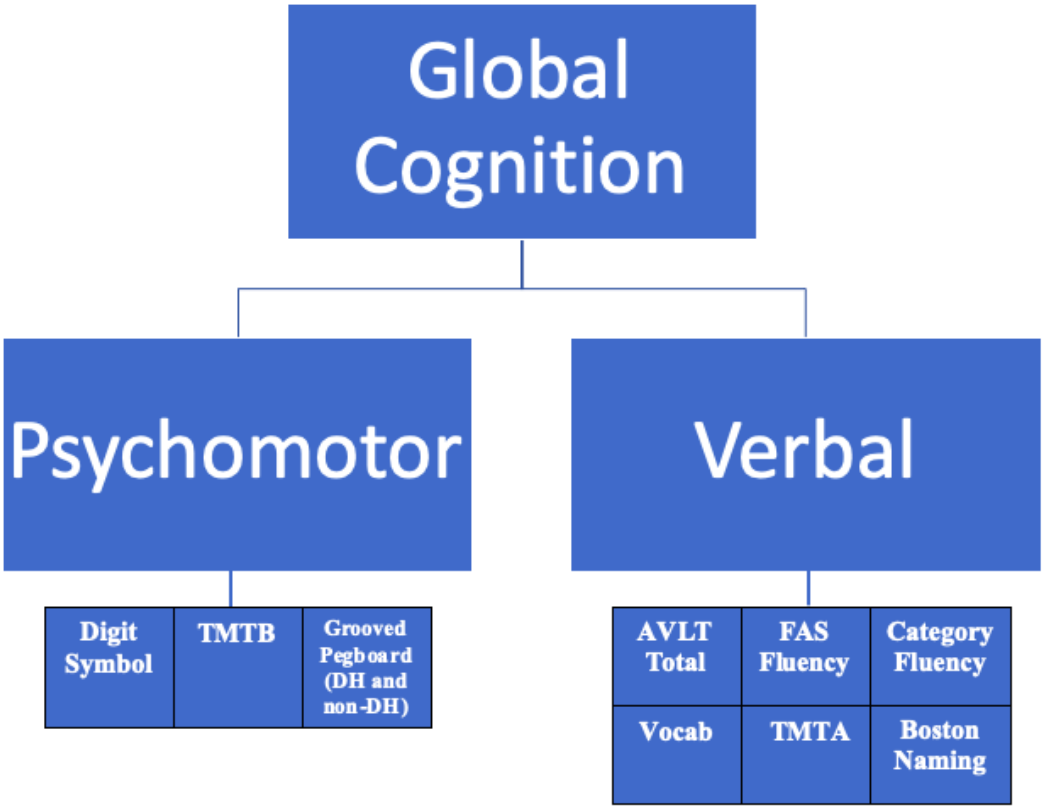

Figure 1. Display of test aggregates for neuropsychological domains

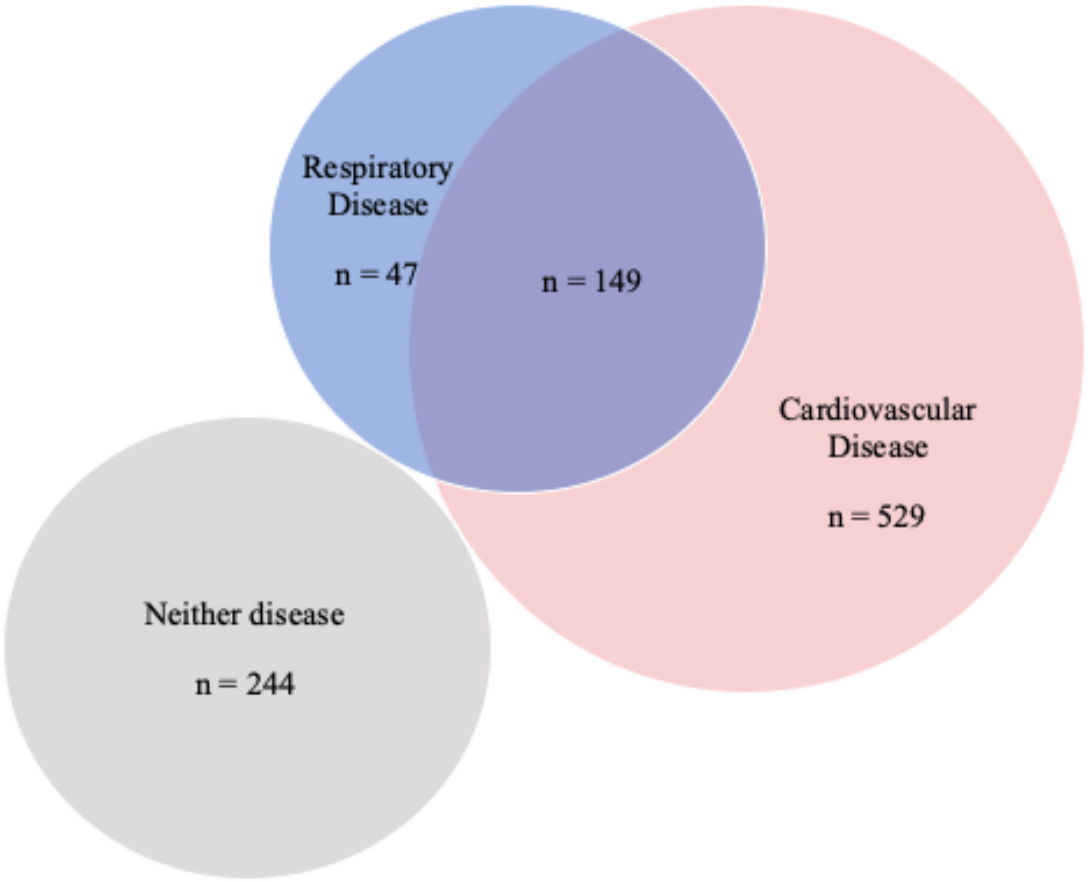

Figure 2. Number of participants with and without diagnoses of cardiovascular and respiratory disease.

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