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Association between Depression and Subjective Cognitive Function: The Emory Healthy Aging Study

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Bachelor of Science
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Abstract

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By Priscilla Davidson

Depression and cognitive impairment, including dementia, frequently co-occur. It is unclear whether depression is a risk factor, a consequence of cognitive impairment, an independent comorbidity, or a prodrome. Evaluating this association may help clarify the association between depression and cognitive health. We evaluated this association with data from the Emory Healthy Aging Study, a prospective cohort of community-dwelling adults primarily in the Atlanta area aimed at identifying predictors of healthy aging and age-related diseases. An online survey collected baseline information on demographic, socioeconomic, health behavior factors, and personal health history. Current depression was measured using the validated Patient Health Questionnaire-8 with scores ranging between 0-24 (≥10 indicating current depression). Age at depression diagnosis was self-reported and categorized as age ≥30, 31-50, or ≥51 years. Subjective cognitive function (CFI) was measured using the validated Cognitive Function Instrument with scores ranging between 0-14 (lower scores suggesting less impairment). The association between current depression and CFI score, excluding people with a history of depression, mild cognitive impairment or Alzheimer's disease, was assessed using linear regression, adjusting for demographic, socioeconomic, health behaviors, cardiovascular disease and risk factors, concussion history, and kidney disease. The association between a history of depression by age at diagnosis and CFI score, excluding people with mild cognitive impairment or Alzheimer's disease, was assessed using linear regression, adjusting for demographic, socioeconomic, health behaviors, cardiovascular disease and risk factors, concussion history, and kidney disease. In 3,187 participants, current depression was associated with a 3.41 greater CFI score as compared to those without current depression (95% CI 3.07, 3.74). In the final models, age at depression diagnosis at ≤ 30 years old, 31-50, or ≥ 51 years old, was associated with a 1.30 (95% CI 0.88, 1.71), 0.74 (95% CI 0.39, 1.10), or 0.91 (95% CI 0.35, 1.47) higher CFI score, respectively. There is an association between both current and history of depression, at any age, with subjective cognitive function. There appears to be no linear association between age at depression diagnosis and subjective cognitive function. We did not definitively identify the direction of the relationship between depression and cognitive function.

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Background

While many conditions are common to those in the aging population, both depression and cognitive impairment, including dementia, frequently occur in conjunction with one another. The association between depression and dementia is not understood satisfactorily despite the frequency of concurrence. Current literature is in disagreement concerning the association between the two conditions, whether or not depression is a risk factor, consequence of dementia, independent comorbidity, or a prodrome [1]. Evidence suggests that there is an increased risk of dementia in patients with depression [2, 3]. Meanwhile, other evidence demonstrates the opposite and have evidence that suggests that depression is not a risk factor for dementia [4, 5].

This paper will explore this relationship in order address the discrepancy between current published studies. We aim to determine the association between depression and subjective cognitive impairment as a predictor of dementia in 2,926 to 3,187 patients in the Emory Healthy Aging Study of primarily patients of Emory Healthcare in Atlanta, Georgia. The association will be assessed by current depression and a history of depression to determine the direction of the association with subjective cognitive impairment.

Depression

Depression is an important public health problem in the United States of America as well as around the world. The World Health Organization has predicted that depression will be the leading cause of disease burden by the year 2030 [6]. Depression is one of the most common mental disorders in the United States of America with 1 out of 20 people who were 12 years old and older reporting current moderate to severe

depression in the past two weeks from 2009 to 2012 [6, 7]. According to the Centers for Disease Control and Prevention, depression is one of the leading causes of disease or injury in both males and females worldwide [6]. Approximately ten percent of all adults who are between the ages of 40 and 59 reported currently having depression. According to the National Institute of Mental Health, depression is defined as a common, but serious, mood disorder that negatively impacts daily activities and alters how an individual feels and thinks [8]. Depression is not evenly distributed between the genders, with a larger percentage of females reporting depression than males [6]. Current research indicates that a combination of genetic, biological, environmental, and psychological factors can lead to the development of depression [8]. The diagnosis of depression is made based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM). The DSM-IV criteria for being diagnosed with depression is that a person must experience five or more symptoms from the list for a continuous period of at least two weeks and that these symptoms be routinely present and have an effect on the individual's daily life [9]. The list of symptoms can be found in figure 1.

Cognitive Impairment

Dementia is also an important public health problem and is one of the major causes of dependency and disability worldwide in the older population group [10]. Dementia causes personal suffering, economic loss, and a loss of independence [11]. According to the Centers for Disease Control and Prevention, people with cognitive decline might not be able to take care of themselves or their necessary activities of daily living [12]. According to the World Health Organization, 47.5 million people worldwide have dementia and 7.7 million new cases are diagnosed every year [10]. It is projected

that in 2030, the number of people with dementia will increase to 75.6 million and that by 2050 there will be 135.5 million people with dementia. With the increase in the aging population, the expected number of individuals affected by dementia will increase and, therefore, it is important to understand how depression can affect dementia. However, if there is an association between having depression and the development of dementia, then the treatment of depression could decrease the rates of cognitive decline.

Dementia is defined as a syndrome characterized by cognitive or memory impairments not involving any alteration in consciousness or alertness and impairs an individual's ability to perform activities of everyday living [11]. The impairment in an individual's the ability to perform activities of everyday living is what differentiates dementia from Mild Cognitive Impairment. However, dementia does not refer to a single disorder; rather, it concerns a number of different syndromes commonly linked by behavioral, cognitive, and emotional impairments. A significant, and easily studied, component of dementia is the presence of cognitive impairment. When there is cognitive impairment in dementia, it is described as possibly including memory loss, failure to identify objects, failure to recognize objects, difficulty in understanding words, difficulty in using words, and not being able to carry out motor activities in spite of having sufficient motor function [10, 11]. While dementia is an overarching diagnosis, there are varying forms that include dementia, Alzheimer's disease, vascular dementia, frontotemporal dementia, and Lewy body dementia. It is also very common for the characteristics of one or more types of dementia to occur simultaneously, referred to as mixed dementia.

There is an intermediate clinical phenotype between normal ageing and dementia that is referred to as mild cognitive impairment [13]. However, not all mild cognitive impairment will progress into dementia and some individuals can revert back to normal aging. Subjective cognitive decline is an early risk factor for Alzheimer's disease and dementia and is thought to occur before mild cognitive impairment [14, 15]. Subjective cognitive decline has no identifiable cognitive impairment; however, the individual still reports changes. Also, the evidence suggests that consistently reported, over time, subjective cognitive decline is associated with an increased risk of Alzheimer's disease dementia [16]. Evidence has suggested that subjective cognitive function decline is a sensitive measure to infringing Aβ-amyloid (amyloid-β (Aβ 42)) and neurodegeneration [17, 18].

Association between Depression and Cognitive Impairment

There is evidence that depression is an independent risk factor for dementia. The study by Li et al. was a prospective cohort study of 3,410 people aged 65 and older, without dementia at baseline, living in the Seattle, Washington area [5]. Whether or not a participant had depression at baseline was assessed with the Center for Epidemiologic Studies Depression scale and a history of depression was assessed by questionnaire that included information on age of onset of depression, the severity, and if and what treatment was received. This study had an average of 7.1 years follow-up for participants in which nineteen percent developed dementia. The authors concluded that there is an association between having depression later in life and developing dementia. Reporting depressive symptoms at baseline was associated with a 71% greater relative risk of dementia (HR=1.71, CI: 1.37, 2.13) after adjusting for age-at entry, gender, education,

and wave of enrollment than those without depressive symptoms at baseline. Participants reporting late-life depression was associated with a 46% greater relative risk of dementia (HR=1.46, CI: 1.16, 1.84) after adjustment compared to participants without a history of depression. No increased risk of dementia was found for early-life depression (HR=1.10, CI: 0.83, 1.47). The study by Martinez et al. was a door-to-door population based study of 1,931 people who were aged sixty-five and older in Munguialde, Spain [3]. This study found that depression was associated with both dementia, Alzheimer's disease, and other dementias (OR= 3.08, 95% CI: 1.50, 6.29; OR= 3.19, 95% CI: 1.46-6.98; OR=2.43, 95% CI: 0.31, 18.89). In addition to depression, increasing age (OR= 1.14, 95% CI: 1.11, 1.17), female sex (OR=1.67, 95% CI: 1.14, 2.45), history of stroke (OR=7.84, 95% CI: 1.11, 1.17) and current depression (OR=53.08, 95% CI: 1.50, 6.29) were also risk factors for dementia, however, stroke was only a risk factor for vascular dementia. The study by Saczynski et al. was a study of 949 people using the prospective cohort data from the Framingham Heart Study with a 17 year follow-up [19]. This study found that the currently depressed patients had an increase in the relative risk of developing dementia and Alzheimer's disease than those without depression (HR= 1.72, 95% CI: 1.04, 2.84; HR= 1.76, 95% CI: 1.03, 3.01). These results were similar to the people who are taking antidepressant medication when treated in the model as depressed. There was a dose-response like increase for the risk of dementia and Alzheimer's disease for each 10-point increase on the Center for Epidemiologic Studies Depression Scale (HR= 1.46, 95% CI: 1.18, 1.79; HR= 1.39, 95% CI: 1.11, 1.75).

There is evidence that in the setting of dementia, depression is a risk factor for more rapid cognitive decline in a study that found that depression increases the rate of

cognitive decline in those who already have dementia. that The study by Rapp et al. was a prospective cohort study of 313 nursing home residents in New York and New Jersey that have dementia [20]. Cognitive function was measured as cognitive decline by the change in the Mini-Mental State Examination scores over a 36 month time period, as well as by the Clinical Dementia Rating scales, neuropsychological evaluations (when possible), and interviews using the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders-III-R or DSM-IV. The evidence suggests that when a participant has dementia and depression, this corresponds to an acceleration in their cognitive decline (β = -2.72, SE= 0.65). This trend was observed after adjustment for the level of education and gender. There is significant interaction between depression and dementia suggesting that depression in the presence of dementia further accelerates cognitive decline.

A few different biological pathways have been proposed to explain the association between depression and dementia. Depression is thought, by Ganguli et al, to be due to multiple factors interacting together throughout a lifetime to increase the risk of dementia [21]. Leonard et al. found a link between the neuronal loss in both dementia and depression [14]. When macrophages, in the blood, and microglia, in the brain, are activated, release of pro-inflammatory cytokines follows. These cytokines cause inflammation and an over secretion of cortisol. Cortisol is responsible for inhibiting protein synthesis and that does not allow neurons to be repaired. The failure of repairing neurons can lead to a loss of cognitive function. It is also believed that hypercortisolemia can cause damage to the hippocampus of the brain which could have an effect in Alzheimer's disease because it would decrease the hippocampus's ability withstand the neurodegeneration. Zverova et al found that the level of plasma cortisol mirrors the

degree of cognitive impairment found in Alzheimer's disease [22]. They also found that hypercortisolemia and hypocortisolemia are associated with depressive disorder in this cohort. Hypercortisolemia in the plasma was significantly associated with Alzheimer's disease and is a biomarker. In this instance, the depression did not directly cause dementia but made the person more susceptible to dementia.

An association between depression and dementia provokes the question of whether the treatment of depression would alleviate cognitive impairment. Nebes et al. as well as Bhalla et al address this question in their respective studies. The study by Nebes et al. had 73 patients diagnosed with geriatric depression, already enrolled in a randomized double-blind clinical trial comparing the tricyclic antidepressant, nortriptyline, or the selective serotonin reuptake inhibitor, paroxetine, as a treatment for late-life depression in Pittsburgh, Pennsylvania [23]. The study found when a patient underwent treatment for depression, the cognitive function of the patients improved as the depression improved. However, there remains a lingering residual amount of cognitive dysfunction that continues even after treatment. The evidence also suggests this in a clinical trial study of late life depression by Bhalla comparing treatment (low dose lorazepam, open-label treatment, and paroxetine) and a placebo of 96 people without dementia at baseline in Pittsburg, Pennsylvania [24]. In this study, older people with cognitive impairment and depression, who underwent treatment for depression, continued to have cognitive impairment after their depression was in remission. The authors also concluded that the older people suffering from depression, but without cognitive impairment, were more likely to have cognitive impairment (23%) a year later even after their depression was in remission compared to non-demented, age and education equal

participants without a history of depression. These studies effectively demonstrate that treatment of depression can have an effect on cognitive impairment. However, the treatment of depression only resulting in a partial remission of dementia would indicate depression might not be the cause of dementia, or at least not the only cause. Unfortunately, there are weaknesses in the use of these studies in the application of treatment. Primarily, these studies do not account for a temporal relationship in the design; therefore, do not address whether the depression caused the cognitive impairment or if the impairment was preexisting and possibly a cause of the depression. Another weakness is the assumption that treating depression and its remission is the same as never having depression on cognitive function.

There is evidence that depression is a consequence of dementia. The case-control study by Amieva et al found that there was no increase in the self-report of depressive symptoms in the time period after dementia was diagnosed in the PAQUID study, French population-based sample of community dwelling individuals [25]. The study had 350 participants who developed Alzheimer's disease during a 14-year follow up matched to 350 elderly control subjects. A decline in cognitive performances presented up to 12 years prior to dementia measures (semantic memory and conceptual formation) followed by global deficits accompanied by an increase in symptom s of depression and memory complaints. Due to the cognitive dysfunction, around 2 years later, the participants had slight dependency in activities of daily living. The later 3 years had a significant worsening in impairment that progressed until the participants developed dementia.

Depression may be a psychological response to dementia [21]. This response could be due to a person being self-aware of having mild cognitive impairment that has

not yet begun to disrupt their ability to function on a daily basis. If a person with mild dementia recognizes that something is wrong but cannot recognize the cause, they may start to feel depressed. When dementia makes activities no longer as enjoyable as they once were and makes everyday tasks challenging, this can lead to depression or the impression of depression when the person stops doing these tasks or activities. As dementia progresses, the person can realize what is wrong and become depressed at the thought of having dementia. This serious effect on mood can be attributed to dementia being a progressive disease that currently has no cure in which the individual will lose their function. However, it is postulated that, in persons whose dementia includes a loss of insight, or anosognosia, those individuals may not show signs of depression.

There are also evidence some studies that suggest that there is no association between depression and dementia and they are independent comorbidities. The study by Luppa et al. was a prospective cohort of 1,265 people who are aged 75 years old and older in Germany with one and a half year follow-ups for 8 years [4]. They found that there was a significant association between incident dementia and depressive symptoms, especially mood-related. However, after controlling for sociodemographic, cognitive, and functional impairment, this association was no longer present and no other clear associations were found. However, the study is adjusting for components of diagnostic criteria for dementia. The study by Heun and Hein is a follow-up from a previous cross-sectional study of 1,431 elderly people who did not have depression in the initial study in Germany [26]. The authors conclude that dementia and mild cognitive impairment are a risk factor for developing depression but that it was not a risk factor when the model controlled for age, female gender, subjective memory impairment, lifetime diagnoses of

anxiety disorders, and somatoform disorders. The study from Li et al. also found that there was no association between having early-life depression and the risk of dementia [5].

When there is no observed association between depression and dementia, they can still be regarded as comorbidities. This can be seen in people who have a history of early-life depression with reoccurrences and, later in life, develop dementia [21]. One pathway in which depression and dementia are comorbid, but could still affect each other, is based upon the theory of cognitive reserve [27]. The theory of cognitive reserve asserts that individuals have a backup capacity of cognitive function, which can allow them to compensate for neuropathology and damage adequately enough to continue functioning within a normal range. Specifically, cognitive reserve is the brain actively trying to counteract pathology and damage. This theory of cognitive reserve, applied to depression and dementia, suggests that depression compromises the cognitive reserve and allows for the symptoms of dementia to be expressed earlier than if depression were not present.

There is also evidence in certain studies to suggest that depression is a prodrome of dementia. The study by Ganguli et al. is a prospective cohort of 1,265 people age 67 and older without dementia at baseline in a rural southwestern Pennsylvania. The participants were followed for 12 years [28]. This found depression and cognitive decline were associated with each other but that future decline in cognitive function was not predicted by depression. They found that in the dementia-free group, there was a very small decline in cognition; however, there was a larger decline in the group that would eventually develop dementia. This implies that the future cognitive decline was found to not be due to depression but, instead, to be a prodrome of incipient dementia. The study

by Chen et al. used an earlier version of the cohort above and found that when looking at the time relationship between depression and dementia onset that depression is a prodrome of Alzheimer's disease and not a predictor or comorbidity [29]. A study by Barnes et al. is a retrospective cohort study of 13,535 people who are a part of Kaiser Permanente Medical Care Program of Northern California looking at depressive symptoms in mid-life and late-life [30]. The authors concluded that late life depression might be a prodrome of Alzheimer's disease.

Several possibly pathways have been proposed to explain the assertion that depression is a prodrome of dementia. One possible pathway is that dementia could cause disruptions in the serotonergic and noradrenergic systems, which could lead to the appearance of depressive symptoms [21]. Another possibility is that the emotional impairment from dementia is observed before other symptoms are discovered. This symptom of dementia can be mistaken to be depression.

While there is robust amount of research on the association between depression and dementia, there is not a consensus on the direction of association and more research is necessary. One reason for the difference in associations presented by various studies could be that the populations studied are responsible. A portion of the studies, in which the authors concluded no associations, are primarily German-based cohorts. The variation in these cohorts, both those demonstrating associations and those that do not, could be indicative of the differences in the populations but not necessarily the association.

There is gap in literature is about which way the relationship between depression and cognitive impairment goes. There is recent literature suggesting that subjective cognitive complaint may signal the earliest stage of cognitive impairment. The aims of

this thesis are to evaluate the association between current depression and subjective cognitive impairment and to evaluate the association between age at depression or bipolar disorder diagnosis and subjective cognitive impairment.

Methods

Data Collection

The Emory Healthy Aging Study, an ongoing prospective cohort aimed at recruiting 100,000 men and women, is a clinical research study, collecting data by an online questionnaire targeting people in the metro Atlanta area. The Emory University Institutional Review Board approved the study protocol and all participants provided informed consent to be a part of the study. Secondary analysis was deemed exempt from human subjects approval by the Emory Institutional Review Board (see appendix). Participant recruitment began in 2015 through multiple channels, including face-to-face interactions with study staff in the Emory Healthcare Clinic waiting areas, informational kiosks placed in Emory hospital and clinic waiting rooms, informational letters co-signed by prospective participants' primary care provider and study principle investigators, recruitment emails for prospective participants in the Emory Healthcare network with no mailing address, and community events such as charity walks, health forums, and faith-based gatherings to inform prospective participants. Due to this form of recruitment, the participants of this study are mainly Emory patients, their spouses, family members, and associated non-relatives. To be eligible for the study participants had to be 18 years old or older, residing in the United States of America, able to understand and read English, and agree to be contacted for future studies.

The online questionnaire includes a Health History Questionnaire (HHQ) to gather demographic information, general health and well-being, physical activity, smoking, self-reported medical and family history, and participant contact information. There is a psychosocial assessment in the Health History Questionnaire section that includes the Cognitive Function Instrument (CFI) self-report to assess subjective

cognitive function, the Patient Health Questionnaire-8 (PHQ-8) to measure depression, and the Generalized Anxiety Disorder-7 Questionnaire (GAD-7) to measure anxiety [15]. The questions on physical activity were about the duration and frequency of mild, moderate and strenuous exercise.

Assessment of Depression

Depression was assessed by self-report using the Patient Health Questionnaire-8 which uses the same questions as the Patient Health Questionnaire-9 without the question about thoughts of death or self-harm [31]. The Patient Health Questionnaire-9 is a part of the PRIME-MD diagnostic instrument for common mental disorders and has been found to be a reliable and valid measure of the severity of depression [31, 32]. The Patient Health Questionnaire-8 is comparable to the Patient Health Questionnaire-9 for diagnosing depressive disorders with the DSM-IV criteria. A very high correlation has been found between using the Patient Health Questionnaire-8 and Patient Health Questionnaire-9 in different studies (r=0.997 and r=0.998). The Patient Health Questionnaire-8 identifies depression in the past 2 weeks. The questionnaire is comprised of 8 items that are summed together for the total score, ranging from 0-24, each of which are scored by: Not at all=0, Several days=1, More than half the days=2, and Nearly every day=3. A Patient Health Questionnaire-8 score of 10 or greater indicated current depression. The questionnaire used for the Patient Health Questionnaire-8 is found in appendix A. Age at depression or bipolar disorder diagnosis was evaluated by self-reported medical history. The age of diagnosis of depression or bipolar disorder were under 30, 30-40, 41-50, 51-60, 61-70, and over 70 years old. These categories were

collapsed into three age categories which are 30 years old or less, 31 to 50 years old, and 51 years old or older.

Assessment of Subjective Cognitive Function

Subjective cognitive impairment was assessed using the self-report version of the Cognitive Function Instrument developed by the Alzheimer's Disease Cooperative Study [15]. The Cognitive Function Instrument can detect early changes in subjective cognitive and functional abilities of patients at the earliest stages of disease. The questionnaire is comprised of 14 items regarding perceived memory decline, cognitive difficulties, and functional abilities over the past year. The Cognitive Function Instrument score is the sum of all the responses, ranging from 0-14, each of which is scored based upon the answers by: No=0, Maybe=0.5, and Yes=1. Lower scores suggest less self-reported impairment. The questionnaire used for the Subjective Cognitive Function can be found in appendix B.

Assessment of Covariates

The variables examined as covariates are all found to be associated or confounders in the literature. Cooper et al found evidence for the inclusion of diabetes, and heavy alcohol use [33]. Xu et al found evidence for the inclusion of hypertension, type 2 diabetes mellitus, heart disease, low education, high body mass index, smoking, and light-to-moderate drinking [34]. The other covariates were found to be necessary in the papers in the background section. The covariates in the analysis, all assessed by questionnaire, include: age at baseline, gender, self-reported race, educational attainment, household income, exercise, whether or not the participant has smoked, alcohol consumption, BMI, hypertension, whether or not the participant has diabetes, history of

having coronary artery disease, history of having a stroke, history of a concussion, and whether or not the participant has kidney disease. Age at baseline was given in the questionnaire. Gender was self-reported as male or female. Race was self-reported by selecting all races that apply from White, Black/African American, American Indian/Alaska Native, Asian, and Native Hawaiian/Other Pacific Islander. Anyone who selected more than one race were compiled into a category called Multi-racial. Educational attainment is obtained by asking for the highest degree or level of school completed from Less than high school, High school diploma / GED, Some college credit, but no degree, Associate's degree (e.g. AA, AS), Bachelor's degree (e.g. BA, BS), Master's degree (e.g. MA, MS, MBA), and Professional or doctorate degree. Household income was assessed by total income during the last 12 months by categories $29,999 or less, $30,000-$39,999, $40,000-$49,999, $50,000-$59,999, $60,000-$74,999, $75,000-$99,999, $100,000-$149,999, and $150,000 or more. Exercise was assessed by asking how often each week the participant does moderate or strenuous exercise (for example , biking outdoors, using an exercise machine (like a stationary bike or treadmill), aerobics, swimming, folk or popular dancing, jogging, tennis) in the categories of None, 1 day per week, 2 days per week, 3 days per week, 4 days per week, and 5 or more days per week. Whether or not the participant has ever smoked was assessed by asking if they had ever smoked cigarettes regularly with two options of yes or no. Alcohol consumption was assessed by asking during the past 12 months how often the participant usually has any kind of drink containing alcohol (by a drink we mean half an ounce of absolute alcohol (e.g. a 12 ounce can or glass of beer or cooler, a 5 ounce glass of wine, or a drink containing 1 shot of liquor)). The categories to choose from were no drinks in the past

year, 1 to 2 times in the past year, 3 to 11 times in the past year, once a month, 2 to 3 times a month, once a week, twice a week, 3 to 4 times a week, 5 to 6 times a week, and every day. For analyses, the categories were collapsed into never drinkers, moderate drinkers who have less than 6 or more drinks a year, and heavy drinks who have 6 or more drinks a week. Body Mass Index (BMI) was calculated from the weight and height participants reported. Hypertension, diabetes, and coronary artery disease were assessed by asking a participant if a doctor has ever told them they have any of the following conditions and to indicate at which age they were told of the condition, with High blood pressure (Hypertension), Diabetes, and Coronary artery or coronary heart disease (includes angina) Diabetes as a few of the options. The age of diagnosis categories were under 30, 30-40, 41-50, 51-60, 61-70, and over 70 years old.

Participants

All individuals who gave information on the PHQ-8, the CFI, age at depression diagnosis and important covariates in the Emory Healthy Aging Study questionnaire will be included. The covariates, based upon a literature review are age at baseline, gender, self-reported race, educational attainment, household income, exercise, whether or not the participant has smoked, alcohol consumption, BMI, hypertension, whether or not the participant has diabetes, history of having coronary artery disease, history of having a stroke, history of a concussion, and whether or not the participant has kidney disease.

Two separate subsets of the participant data of 4,148 people were used for analysis. Data from 2,926 participants was included in the analysis evaluating the association between current depression subjective cognitive impairment in those with no self-reported history of depression or bipolar disorder Data from 3,187 participants, were

used to evaluate the association between age at depression or bipolar disorder diagnosis and subjective cognitive impairment, in those without a diagnosis of mild cognitive impairment or dementia.

Analysis

Participants who supplied demographic information in the questionnaire, completed the self-report cognitive function instrument portion of the questionnaire, and completed the health history portion of the questionnaire were used to create the models. For each of the two associations of interest evaluated, the participant characteristics were compared by exposure status; either by current depression status or by age at diagnosis of depression or bipolar disorder using t-tests, ANOVA, or chi-squared tests according to variable distribution.

To examine the association between current depression and subjective cognitive impairment, we ran a linear regression models with a primary independent variable of current depression and the Cognitive Function Instrument total score as the outcome variable. We also ran a linear regression models to evaluate the association between the age at diagnosis of depression or bipolar disease and Cognitive Function Instrument total score. The age groups used for the age of diagnosis of depression or Bipolar disorder analysis were: never diagnosed, diagnosed at 30 years old or younger, diagnosed between 31 and 50 years old, and diagnosed at 51 years old or older. Furthermore, the analysis for the association between the age at diagnosis of depression or bipolar disease and Cognitive Function Instrument total score was also assessed by stratification upon current depression status. We evaluated covariates in the model for confounding and effect measure modification. Both models were sequentially adjusted for groups of related

covariates. The groups of related covariates were demographic factors (age at baseline, sex, self-reported race), sociodemographic factors (education, household income), health behavior factors (physical activity, smoking status, alcohol consumption), cardiovascular disease risk factors (BMI, hypertension, diabetes), cardiovascular disease (coronary artery disease, stroke), concussion history, and kidney disease. All data analysis was completed in SAS 9.4.

Results

Characteristics of Participants without History of Depression or Bipolar Disorder

We included 2,926 participants in the first analysis, which evaluated the association between current depression and subjective cognitive impairment in those without a history of depression or bipolar disorder. Of these 2,926 participants, 2,826 (96.6%) participants did not have current depression and 100 (3.4%) participants were currently depressed (Table 1). The mean age of non-depressed participants was 58.7 (standard deviation (SD) = 12.7) compared to currently depressed participants whose mean age was 53.4 (SD= 14.6) years old. Women constituted a slightly greater proportion of those reporting current depression (77.0%) than women who did not report current depression (74.6%).The majority of participants self-identified as white. Whites were more likely to not meet criteria for current depression, whereas the proportion of those who were currently depressed self- identified as black/African American, Asian, American Indian/Alaska Native, or multiracial as compared to those who did not meet criteria for current depression. No participants who identified as Native Hawaiian/Other Pacific Islander met criteria for current depression, however there were only seven such participants in this analysis.

In this analysis, self-reported income and educational attainment were the covariates used to assess socioeconomic status. Overall, participants in the Emory Healthy Aging Study reported high household incomes, with the largest proportion of the reported household income distribution at 150,000 dollars or greater, with a larger proportion of not currently depressed participants than currently depressed participants in that group. The proportion of currently and not currently depressed participants remained

fairly equal as reported household income decreased through the 50,000 to 59,999 dollar group. In the lowest household income groups, there was a greater proportion of participants who met criteria for current depression than did not, with the exception of those in the 30,000 to 39,999 dollar income group. Examining educational attainment in the Emory Healthy Aging Study, the largest proportion of participants obtained a Bachelor's degree, followed by a Master's degree, a professional or Doctorate, then some college without a degree, an Associate's degree, high school diploma or less than a high school diploma. Compared to participants not meeting criteria for current depression, a smaller proportion of participants meeting criteria for current depression obtained at least a Master's degree. Conversely, a greater proportion of those with current depression held a Bachelor's degree or less education.

Health behaviors of interest in this analysis were frequency of physical activity, alcohol consumption, and smoking status. The most commonly reported frequency of exercise was three days per week, followed by not exercising. Fewer participants reported exercising fewer than three times per week. A greater proportion of those who did not meet criteria for current depression exercised three or more days per week as compared to those meeting criteria for current depression. In contrast, there was a greater proportion of participants meeting criteria for current depression who exercised one or fewer days per week than those who did not meet criteria. Most participants in the Emory Healthy Aging Study reported moderate alcohol consumption, with roughly the same proportion of participants reporting no or heavy alcohol consumption. The proportion of those meeting criteria for current depression who reported no alcohol consumption was greater than those who were not currently depressed. Among those who did not meet criteria, a

greater proportion reported any alcohol intake. Smoking status was defined as ever smoker, including current and former smokers, versus never smokers. The proportion of ever smokers was approximately equal among those with current depression and those without.

Among the cardiovascular risk factors included in this analysis, there was no difference in the proportion of participants with and without current depression who reported a history of hypertension or diabetes, though mean BMI was higher in those with current depression. . The average body mass index (kg/m^2) for non-depressed participants is 26.6 (SD= 5.4), for the depressed participants is 29.2 (SD= 7.0), which is considered overweight for both. Similarly, there was no difference in the proportion of participants with and without current depression who reported a history of coronary heart disease, stroke, or history of concussion, though there was a greater proportion of participants with a history of renal disease among those with current depression as compared to those without.

Characteristics of Participants without History Dementia

We included 3,187 participants in the first analysis, which evaluated the association between having a history of diagnosed depression and subjective cognitive impairment in those without a history of cognitive impairment. Of these 3,187 participants, 2,923 (91.7%) participants have never been diagnosed with depression, 86 (2.7%) participants have been diagnosed with depression at 30 years old and younger, 127 (4.0%) participants have been diagnosed with depression between 31 to 50 years old, and 51(1.6%) participants have been diagnosed with depression at 51 years old and older (Table 2). The mean age of never diagnosed with depression participants was 58.5

(SD=12.8), depression at 30 years old and younger was 48.2 (SD= 14.0), diagnosed between 31 to 50 years old was 60.0 (SD= 8.2), and diagnosed at 51 years old and older was 66.2 (SD= 6.1). Women constituted a slightly greater proportion of those reporting a history of depression at 30 years and younger (88.4%), then women diagnosed between 31 to 50 (85.8%), then women never diagnosed (74.7%), and lastly women diagnosed at 51 and over (74.5%). The majority of participants self-identified as white. Whites were more likely to not meet criteria for no history of depression, whereas the proportion of those who have a history of depression self- identified as black/African American, Asian, American Indian/Alaska Native, or multiracial as compared to those who did not meet criteria for having a history of depression. No participants who identified as Native Hawaiian/Other Pacific Islander met criteria for having a history depression, however there were only seven such participants in this analysis. In addition, no participants who identified as American Indian/Alaska Native met criteria for having a history depression for the under 30 and over 51 age groups; however, there were only twenty-three such participants in this analysis.

In this analysis, self-reported income and educational attainment were the covariates used to assess socioeconomic status. Overall, participants in the Emory Healthy Aging Study reported high household incomes, with the largest proportion of the reported household income distribution at 100,000-149,999 with a larger proportion of a history of depression at 31-50 participants then a history of depression at 30 or younger, then 51 and over, and lastly never diagnosed with a history of depression. The proportion of the varying groups that have a history of depression and not having a history of depression participants remained fairly equal as reported household income decreased

through the 50,000 to 59,999 dollar group. In the lowest household income groups, there was a greater proportion of participants who met criteria for having a history of depression than did not have a history of depression, with the exception of those in the 30,000 to 39,999 dollar income group. Examining educational attainment in the Emory Healthy Aging Study, the largest proportion of participants obtained a Bachelor's degree, followed by a Master's degree, a professional or Doctorate, then some college without a degree, an Associate's degree, high school diploma or less than a high school diploma. Compared to participants not meeting criteria for current depression, a smaller proportion of participants meeting criteria for current depression obtained at least a Master's degree. Conversely, a greater proportion of those with current depression held a Bachelor's degree or less education.

Health behaviors of interest in this analysis were frequency of physical activity, alcohol consumption, and smoking status. The most commonly reported frequency of exercise was not exercising, followed by exercising 2 days a week. A greater proportion of those who did not have a history of depression exercised three or more days per week, which was equivocal to participants with a diagnosis history at 31-50 as compared to those with other ages of diagnosis. In contrast, there were a greater proportion of participants with a history of depression aged 30 and under and 31-50 who exercised one or fewer days per week than those who did not have a history of depression and diagnosed at 51 and older. Most participants in the Emory Healthy Aging Study reported moderate alcohol consumption. The proportion of those who reported heavy alcohol consumption was greater in those diagnosed with depression at 51 and over and decreases for each age group at diagnosis and then for those who do not have a history of

depression. Among those who have a history of depression at any age, a greater proportion reported any alcohol intake than those who have no history of depression. The proportion of ever smokers was equal among all age groups with a history of depression and those without a history of depression.

Among the cardiovascular risk factors included in this analysis, there was a dose response type difference that decreased with decreasing age of diagnosis and no history of depression in the proportion of participants who reported a history of diabetes, kidney disease, and mean BMI with all groups being considered overweight with the exception of 51 and over which is obese. There was a dose response type difference in stroke history that increased with increasing of no history through over 51 with the largest proportion being over 51. A history of hypertension and coronary artery disease have the same proportions with the greatest being over 51, then 31-50, then no history of depression, and finally 30 and younger. The largest proportion of participants with a history of concussion was in people with a history of depression compared to not having a history of depression.

Association between Current Depression and Subjective Cognitive Impairment

In the unadjusted model evaluating the association between current depression and subjective cognitive impairment in those without a history of depression, current depression was associated with a 3.41 (95% CI: 3.07, 3.74) higher CFI score (Table 3, Figure 2). When age, gender, and race were added to the model, there was no meaningful attenuation of effect estimate. Additional adjustment for socioeconomic factors the association became somewhat less pronounced (percent difference, 6%). Additional covariate adjustment, including health behavior factors, cardiovascular risk factors and

other medical history, did not result in any additional meaningful reduction in the effect estimate. Overall, full covariate adjustment resulted in minimal attenuation of the effect estimate from the unadjusted model (percent difference, 8%). Given the minimal attenuation of the effect estimate with covariate adjustment and 95% confidence intervals of similar width between unadjusted and fully adjusted models, the final model selected was the unadjusted model.

Association between Age at Depression Diagnosis and Subjective Cognitive Impairment

In the unadjusted model evaluating the association between a history of depression and subjective cognitive impairment, a history of depression, with no history of depression as the reference, by age category (30 years old or younger, 31-50 years old, and 51 years) was associated with a higher CFI score of 1.18 (95% CI: 0.79, 1.57), 0.89 (95% CI: 0.56, 1.21), and 1.10 (95% CI: 0.59, 1.61) respectively (Table 4, Figure 3). Based on the fully-adjusted model, there was a modest but statistically significant association between age at depression diagnosis and subjective cognitive impairment in all three age categories. The mean difference in CFI total score was 1.30 (95% CI: 0.88, 1.71), 0.74 (95% CI: 0.39, 1.09) and 0.91 (95% CI: 0.35, 1.47) for those diagnosed with depression at 30 years old or younger, 31-50 years old, and 51 years old or older, respectively. The association strengthened in participants under 30 as additional covariates were added to the model. The association was attenuated in the two older age groups as covariates were added to the model. There was no clear pattern of confounding variables across the different age groups. The difference in the point estimates between the fully-adjusted and the unadjusted models was between 11% and 17% depending on which age group was being addressed. The mean difference in CFI total score was 0.22

(95% CI: -1.17, 1.61), 0.38 (95% CI: -1.21, 1.97) and -0.44 (95% CI: -2.97, 2.08) for those diagnosed with depression at 30 years old or younger, 31-50 years old, and 51 years old or older, respectively for current depression. The mean difference in CFI total score was 1.07 (95% CI: 0.64, 1.50), 0.43 (95% CI: 0.09, 0.77) and 0.65 (95% CI: 0.11, 1.19) for those diagnosed with depression at 30 years old or younger, 31-50 years old, and 51 years old or older, respectively without current depression.

Discussion

In this study, there was a statistically significant linear relationship between current depression and subjective cognitive impairment, such that current depression is associated with a nearly 3.41 points higher total CFI score, when compared to not having current depression, in those without a history of depression. Also, we concluded that there was a statistically significant linear relationship between having a history of depression and subjective cognitive impairment, such that a history of depression is associated with a between 0.74 and 1.30 points higher total CFI score, when compared to not having a history of depression, in those without a history of cognitive impairment. There was found to be a stronger association between having a history of depression and subjective cognitive impairment for participants diagnosed before the age of 30, compared to not having a history of depression than for the other age categories for age a history of diagnosis. When participants had a history of depression but no current depression there was a statistically significant linear relationship, which was found to be stronger in participants diagnosed before the age of 30. There was not significant relationship between having a history of depression and subjective cognitive impairment for participants who have current depression.

The association between current depression and subjective cognitive function was robust to covariate adjustment, with no significant change in the relationship between different models. This could mean the relationship is so strong in our study that no covariate adjustment was necessary to obtain an unconfounded estimate the association. Another possible explanation is that questions on Patient Health Questionnaire-8 and Cognitive Function Instrument are related. There are two questions in particular that

could cause this relationship the Patient Health Questionnaire-8 asks if a participant has "Little interest or pleasure in doing things?" and "Trouble concentrating on things, such as reading the newspaper or watching television?" while the Cognitive Function Instrument asks participants "Are you less involved in social activities?" and "Do you have more trouble following the news, or the plots of books, movies or TV shows, compared to one year ago?". These overlapping cognitive and function questions may be measuring the same psychological state.

There are a few limitations of this study. The analysis uses cross sectional data which makes assessment of causality difficult. There may be residual confounding by unmeasured factors due to this studying being observational. As repeated measures of depressive symptomatology and self-reported cognitive function are collected during the study, using the PHQ-8 and Cognitive Function Instrument, respectively, it will be possible to better describe the temporal progression of depression and self-reported cognitive function. Another limitation is the question of whether or not the Cognitive Function Instrument and Patient Health Questionnaire-8 are associated by having the two similar questions. Future studies that can better describe the associations between items on each scale may improve our understanding of the relationship between depression and cognitive impairment. A third limitation is that our study sample included only those who were able to complete an online questionnaire, which is an example of selection bias within the study. Itis is likely that people who are not comfortable with computers and the internet would not participate. This exclusion of possible participants could have an effect on the results by biasing towards the null. It would be expected that those who did not participate would have a lower socio-economic status and educational attainment and

greater risk for poorer cognitive function. In addition, the demographic and socioeconomic characteristics are not representative of the population as a whole, for example having a higher income and educational attainment, which make the results less generalizable. A fourth limitation is that we lacked information about how long a participants were depressed. It is unknown if participants diagnosed early in life had many episodes of depression or if participants diagnosed later in life might have spent less of their life depressed. A fifth limitation is self-reported data is susceptible to measurement error. Finally, for feasibility reasons, we did not utilize a study partner to report on participant cognitive function, which has been utilized with the Cognitive Function Instrument in the past, though this might have contributed additional useful information.

There are several characteristics of this study that can be regarded as strengths. The first of these is the robust sample size, according to epidemiological standards, of the Emory Healthy Aging Study. Large sample size is important to this analysis to ensure adequate power. Another strength of this study is the use of well-validated instruments to assess depression and subjective cognitive function. Finally, the Emory Healthy Aging Study uses evaluation of potential confounding factors.

Our results suggest an association in age of diagnosis of depression and subjective cognitive function as well as current depression and subjective cognitive function. Finding and treating depression as a risk factor for cognitive impairment could help prevent the onset of cognitive impairment. The results of varying studies suggest different results of treatments of late-life depression on cognitive impairment [23, 24]. More studies are needed to clarify whether treatment of depression helps. A study in

Denmark evidence suggests that long-term treatment of depression with older antidepressants decreases the rate of dementia but there is no association for treatment of depression with other kinds of antidepressants (selective serotonin reuptake inhibitors and nonselective serotonin reuptake inhibitors) [35].

While there is robust amount of research on the association between depression and dementia, there is not a consensus on the direction of association and more research is necessary. One reason for the difference in associations presented by various studies could be that the differences between populations being studied are responsible for the differences in study results. A portion of the studies showing no associations are primarily in German-based cohorts. The variation in these study results could be due to the differences in study populations.

If the observed association between current depression and subjective cognitive impairment, in those who do not have a history of depression, is true, it suggests that a prolonged exposure to depression may not be necessary before subjective cognitive impairment becomes evident. Our finding that history of depression is associated with subjective cognitive impairment, regardless of the age at diagnosis is consistent with evidence that depression is a risk factor for cognitive impairment. In those who were diagnosed with depression before 50 years old, especially those diagnosed before 30, it is unlikely that their depression was due to neurodegeneration and more likely, that depression contributed to the risk of later life cognitive impairment. Associations between history of depression diagnosed at different ages and subjective cognitive impairment may represent different causal pathways. Additional information about the amount of time participants experienced depressive symptoms over their lifetimes would

be informative. If subjective cognitive decline represents early stages of cognitive decline, then the finding that depression is associated with subjective cognitive decline is consistent with the results found by Martinez et al as well as Saczynski et al who found that current depression was associated with developing dementia [3, 19]. The results are partially consistent with the results from Li et al. which also found an association between later in life depression and dementia; however, they did not find as association with early life depression which we did find [5]. The difference in results is possibly because of other factors, possibly geographic risk factors such as the southeastern United States being the stroke belt. The results also differ from the studies by Luppa et al and Huen and Hein who found no association after controlling for cognitive and functional impairment this association was no longer present and no other clear associations were found. Adjusting for the criteria that define the outcome may have led to the appearance of no association.

Future studies should look at the under-researched area considering behavioral pathways between depression and dementia. For example, when a person is able to recognize their own cognitive decline they may become depressed as a result. There also is a need for further long-term prospective studies looking at the treatment of depression in varying stages in life. The effects of that treatment on the prevention or delay of the development of dementia would assist in further understanding the association between dementia and depression.

Finding and treating depression as a risk factor for cognitive impairment could help prevent the onset of cognitive impairment. Studies have shown different results of treatments of late-life depression on cognitive impairment [23, 24]. More studies are

needed to clarify whether treatment helps. A study in Denmark has shown that long-term treatment of depression with older antidepressants decreases the rate of dementia but there is no association for treatment of depression with other kinds of antidepressants (selective serotonin reuptake inhibitors and nonselective serotonin reuptake inhibitors) [35]. Even if there is no causal association between depression and cognitive impairment, such that prevention or treatment of depression would decrease the burden of dementia over time, our findings still have important practical application. Given the correlation between depression and subjective cognitive impairment, it is important that the role of depressive symptoms be considered in the clinical environment where a diagnosis of MCI or dementia may be pursued for patients presenting with subjective cognitive complaints.

We conclude that there was a strong significant association between current depression and subjective cognitive function, such that those with current depression had poorer self-reported cognitive function. Also, there was a modest but significant association between a history of depression at any adult age and subjective cognitive function. There did not appear to be a linear association between age at depression diagnosis and subjective cognitive function, as the magnitude of effect estimates for different age groups did not reflect a clear trend. No linear relationship was found between a history of depression at any adult age and subjective cognitive function in participants who have current depression. A significant relationship exists between a history of depression at any adult age and subjective cognitive function when the participant does not have current depression.

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Tables

Table 1. Participant characteristics in the Emory Healthy Aging Study without history of depression or bipolar disorder by current depression status (N=2,926)

Characteristics	No Current depression Mean (SD) or N (%) N=2826	Current Depression Mean (SD) or N (%) N=100	p-value
Age	58.7 (12.73)	53.4 (14.57)	<0.01
Gender			0.58
Female	2105(74.57%)	77(77.00%)	
Race			0.02
African American*	262 (9.27%)	16 (16.00%)	
American Indian*	20 (0.71%)	2 (2.00%)	
Asian	54 (1.91%)	2 (2.00%)	
Caucasian	2432 (86.06%)	75 (75.00%)	
Multiracial	51 (1.08%)	5 (5.00%)	
Native Hawaiian*	7 (0.25%)	0 (0.00%)	
Income			<0.01
≥29,999	105 (3.94%)	15 (15.79%)	
30,000-39,999	113 (4.24%)	1 (0.04%)	
40,000-49,999	134 (5.03%)	12 (12.63%)	
50,000-59,999	181 (6.79%)	9 (9.47%)	
60,000-74,999	288 (10.81)	10 (10.53%)	
75,000-99,999	381 (14.30%)	13 (13.68%)	
100,000-149,999	612 (22.97%)	20 (21.05%)	
≤150,000	850 (31.91%)	15 (15.79%)	
Education			<0.01
Less than high school	6 (0.21%)	0 (0.00%)	
High school diploma/GED	70 (2.48%)	3 (3.03%)	
Some college credit but no	378 (13.39%)	21 (21.21%)	
degree	165 (5.84%)	11 (11.11%)	
Associate's degree	986 (34.92%)	40 (40.40%)	
Bachelor's degree	799 (28.29%)	16 (16.16%)	
Master's degree	420 (14.87%)	8 (8.08%)	
Professional or doctorate degree			
BMI*	26.55 (5.39)	29.19(7.01)	<0.01
History of Coronary Artery	145 (5.15%)	7 (7.00%)	0.41
Disease			
Has Diabetes	206 (7.32%)	7 (7.00%)	0.91
History of a Stroke	61 (2.16%)	3 (3.00%)	0.57
History of a Concussion	172 (6.09%)	10 (10.10%)	0.11
History of Hypertension	1022 (36.20%)	40 (40.00%)	0.44
Has Ever Smoked	876 (31.00%)	34 (34.00%)	0.52
Exercise			<0.01
None	913 (32.35%)	55 (55.56%)	
1 day per week	319 (11.30%)	13 (13.13%)	
2 days per week	420 (14.88%)	13 (13.13%)	
3 days per week	534 (18.92%)	11 (11.11%)	
4 days per week	286 (10.13%)	4 (4.04%)	
5 or more days a week	350 (12.40%)	3 (3.03%)	

Alcohol Consumption			<0.01
Never	529 (19.27%)	36 (37.11%)	
Moderate	1662 (60.55%)	51 (52.58%)	
Heavy	554 (20.18%)	10 (10.31%)	
Has Kidney Disease	43 (1.52%)	8 (8.08%)	<0.01

*African American= Black/African American, American Indian= American Indian/Alaska Native, Native Hawaiian=Native Hawaiian/Other Pacific Islander, BMI= Body Mass Index

Table 2. Participant characteristics in the Emory Healthy Aging Study without history of dementia by age at depression or bipolar disorder diagnosis (N=3,187)

Characteristics	**Mean (SD) or N (%)**				**p-value**
	Never Diagnosed N= 2,923	**Under 30 N= 86**	**31-50 N= 127**	**51 and Over N= 51**	
Age	58.53 (12.84)	48.24 (13.97)	66.16 (6.14)	66.16 (6.14)	<0.01
Gender					<0.01
Female	2180 (74.66%)	76 (88.37%)	109 (85.83%)	38 (74.51%)	
Race					0.69
African American*	278 (9.51%)	3 (3.49%)	5 (3.94%)	6 (11.76%)	
American Indian*	22 (0.75%)	0 (0.00%)	1 (0.79%)	0 (0.00%)	
Asian	56 (1.92%)	2 (2.33%)	2 (1.57%)	1 (1.96%)	
Caucasian	2504 (85.67%)	78 (90.7%)	115 (90.55%)	43 (84.31%)	
Multiracial	56 (1.92%)	3 (3.49%)	4 (3.15%)	1 (1.96%)	
Native Hawaiian*	7 (0.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Income					<0.01
≥29,999	120 (4.35%)	5 (5.88%)	9 (5.64%)	4 (8.33%)	
30,000-39,999	113 (4.10%)	6 (7.06%)	7 (5.31%)	4 (8.33%)	
40,000-49,999	146 (5.30%)	8 (9.41%)	17 (7.06%)	2 (4.17%)	
50,000-59,999	190 (6.89%)	6 (7.06%)	8 (8.49%)	4 (8.33%)	
60,000-74,999	298 (10.81%)	6 (7.06%)	8 (13.15%)	10 (20.83%)	
75,000-99,999	394 (14.30%)	16 (18.82%)	15 (17.72%)	9 (18.75%)	
100,000-149,999	631 (22.90%)	22 (25.88%)	30 (28.34%)	11 (22.92%)	
≤150,000	864 (31.35%)	16 (18.82%)	29 (37.28%)	4 (8.33%)	
Education					0.84
Less than high school	5 (0.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
High school diploma/GED	73 (2.50%)	2 (2.33%)	5 (3.94%)	0 (0.00%)	
Some college credit but no degree	399 (13.66%)	13 (15.12%)	12 (9.45%)	10 (19.61%)	
Associate's degree	175 (5.99%)	2 (2.33%)	9 (7.09%)	1 (1.96%)	
Bachelor's degree	1026 (35.14%)	30 (34.88%)	40 (31.50%)	15 (29.41%)	
Master's degree	814 (27.88%)	24 (27.91%)	39 (30.71%)	16 (31.37%)	
Professional or doctorate degree	428 (14.66%)	15 (17.44%)	22 (17.32%)	9 (17.65%)	

BMI	26.64 (5.48)	28.00 (7.34)	27.88 (5.97)	30.88 (7.89)	<0.01
History of Coronary Artery Disease	152 (5.22%)	3 (3.49%)	7 (5.56%)	5 (10.00%)	0.42
Has Diabetes	213 (7.31%)	7 (8.33%)	19 (15.20%)	10 (20.00%)	<0.01
History of a Stroke	64 (2.19%)	2 (2.33%)	2 (1.59%)	1 (1.96%)	0.978
History of a Concussion	182 (6.23%)	8 (9.41%)	14 (11.02%)	5 (9.80%)	0.08
History of Hypertension	1061 (36.34%)	24 (27.91%)	58 (45.67%)	37 (72.55%)	<0.01
Has Ever Smoked	908 (31.06%)	35 (40.70%)	45 (35.43%)	22 (43.14%)	0.05
Exercise					<0.01
None	966 (33.10%)	35 (40.7%)	54 (42.52%)	30 (58.82%)	
1 day per week	332 (11.38%)	15 (17.44%)	22 (17.32%)	2 (3.92%)	
2 days per week	432 (14.80%)	13 (15.12%)	14 (11.02%)	8 (15.69%)	
3 days per week	545 (18.68%)	7 (8.14%)	23 (18.11%)	4 (7.84%)	
4 days per week	290 (9.94%)	8 (9.30%)	6 (4.72%)	2 (3.92%)	
5 or more days a week	353 (12.10%)	8 (9.30%)	8 (6.30%)	5 (9.80%)	
Alcohol Consumption					<.01
Never	565 (19.90%)	2 (2.53%)	4 (3.60%)	1 (2.17%)	
Moderate	1710 (60.23%)	60 (75.95%)	77 (69.37%)	28 (60.87%)	
Heavy	564 (19.87%)	17 (21.52%)	30 (27.03%)	17 (36.96%)	
Has Kidney Disease	51 (1.75%)	1 (1.18%)	3 (2.40%)	4 (8.00%)	0.01

*African American= Black/African American, American Indian= American Indian/Alaska Native, Native Hawaiian=Native Hawaiian/Other Pacific Islander, BMI= Body Mass Index

Table 3. Sequentially adjusted mean difference and 95% CI for average Cognitive Function Instrument score by current depression status in participants without a history of depression in the Emory Healthy Aging Study.

Model	Mean difference in CFI* score	95% CI		P-value
		Lower	Upper	
Unadjusted	3.41	3.07	3.74	<.01
+ age, gender, race	3.40	3.08	3.73	<.01
+ income, education	3.20	2.86	3.54	<.01
+exercise, smoke, drink	3.18	2.83	3.52	<.01
+ BMI, hypertension, diabetes	3.17	2.82	3.51	<.01
+ heart disease, stroke	3.17	2.82	3.51	<.01
+ concussion	3.13	2.78	3.48	<.01
+ kidney	3.16	2.81	3.51	<.01

* BMI= Body Mass Index, CFI= Cognitive Function Instrument

Table 4. Sequentially adjusted mean differences and 95% CIs for Cognitive Function Instrument total scores by age at depression or bipolar disorder diagnosis in the Emory Healthy Aging Study.

Model	Under 30				31-50				51 and Over			
	Mean difference in CFI* score	95% CI		P-value	Mean difference in CFI score	95% CI		P-value	Mean difference in CFI score	95% CI		P-value
		Lower	Upper			Lower	Upper			Lower	Upper	
Unadjusted	1.18	.79	1.57	<.01	0.89	0.56	1.21	<.01	1.10	0.59	1.61	<.01
+ age, gender, race	1.36	0.97	1.75	<.01	0.90	0.58	1.22	<.01	1.02	0.51	1.52	<.01
+ income, education	1.27	0.88	1.66	<.01	0.84	0.52	1.17	<.01	1.07	0.56	1.59	<.01
+exercise, smoke, drink	1.28	0.87	1.68	<.01	0.82	0.47	1.16	<.01	0.95	0.41	1.49	<.01
+ BMI, hypertension, diabetes	1.31	0.89	1.73	<.01	0.75	0.39	1.10	<.01	0.93	0.38	1.49	<.01
+ heart disease, stroke	1.31	0.90	1.73	<.01	0.75	0.40	1.10	<.01	0.93	0.37	1.49	<.01
+ concussion	1.30	0.89	1.72	<.01	0.73	0.38	1.08	<.01	0.92	0.36	1.48	<.01
+ kidney	1.30	0.88	1.71	<.01	0.74	0.39	1.10	<.01	0.91	0.35	1.47	<.01

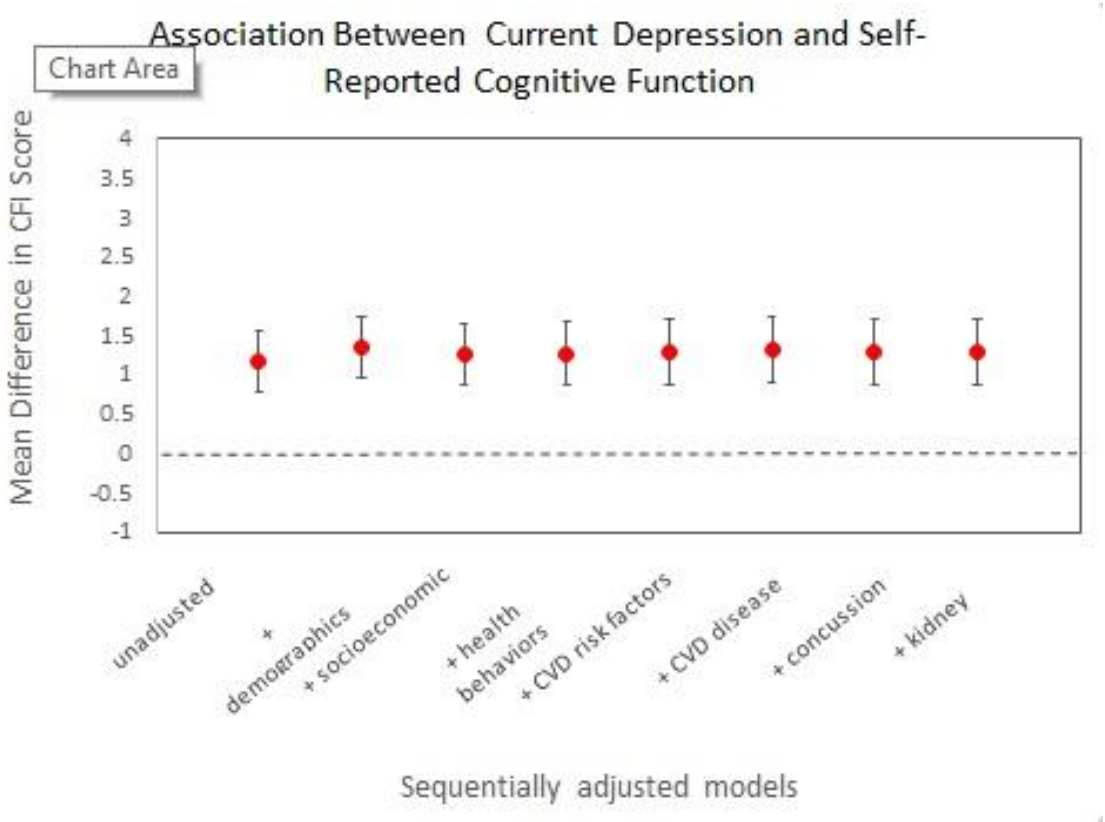
*BMI= Body Mass Index, CFI= Cognitive Function Instrument

Figures

Figure 1. Symptoms of Depression According to the DSM-IV Criteria

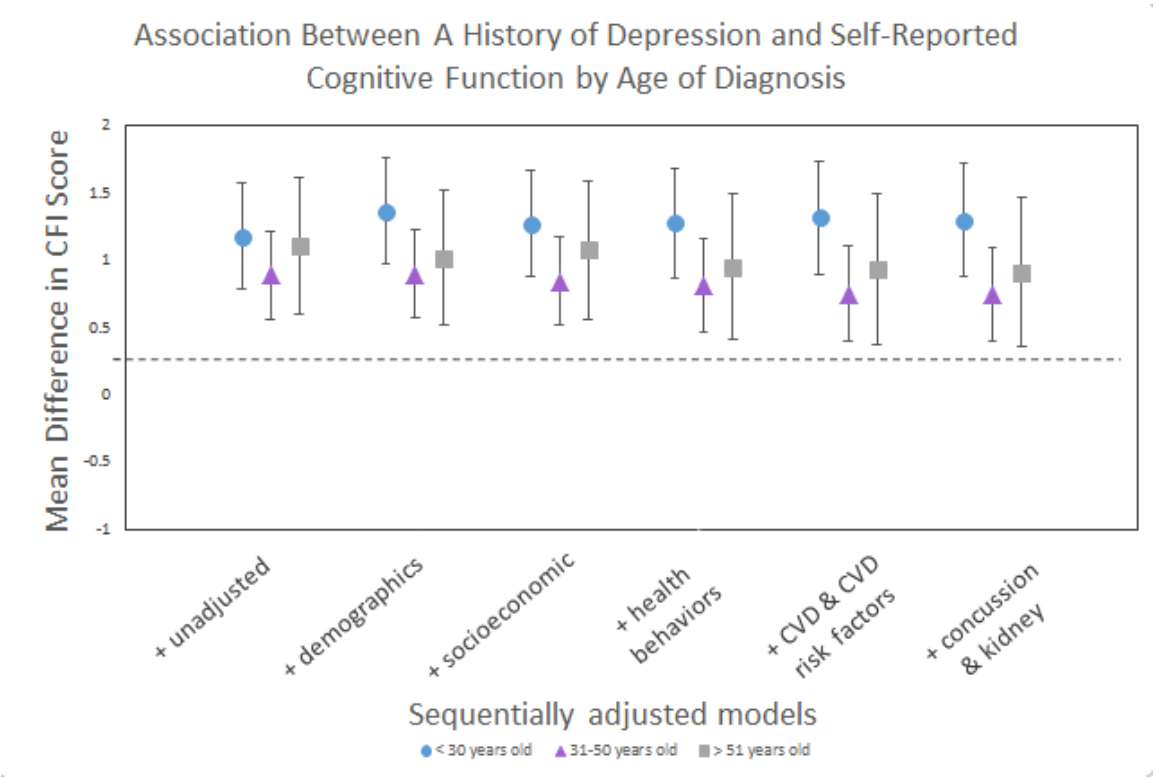
- Feelings of sadness and hopelessness
- Depressed mood
- Loss of interest or pleasure in activities that used to be enjoyable
- Change in weight or appetite (either increase or decrease)
- Change in activity: psychomotor agitation (being more active than usual) or psychomotor retardation (being less active than usual)
- Insomnia or sleeping too much
- Feeling tired or not having any energy
- Feelings of guilt or worthlessness
- Difficulties concentrating and paying attention

Figure 2. Sequentially Adjusted Multivariable Regression Model for Current Depression and Self-reported Cognitive Function



***Demographics**=age at baseline, sex, self-reported race; **Socioeconomic factors**=education, household income; **Health behaviors**=physical activity, smoking status, alcohol consumption; **CVD risk factors** = Body Mass Index, hypertension, diabetes **CVD** = Coronary Artery Disease, stroke

Figure 3. Sequentially Adjusted Multivariable Regression Model for a History of Depression and Self-reported Cognitive Function



***Demographics**=age at baseline, sex, self-reported race; **Socioeconomic factors**=education, household income; **Health behaviors**=physical activity, smoking status, alcohol consumption; **CVD risk factors** = Body Mass Index, hypertension, diabetes **CVD** = Coronary Artery Disease, stroke

Appendices

Appendix A
Patient Health Questionnaire-8 for depression

Over the last 2 weeks, how often have you been bothered by any of the following problems? Please indicate your answer by checking the appropriate box for each question.					
1	Little interest or pleasure in doing things?	Not at all ☐	Several days ☐	More than half the days ☐	Nearly every day ☐
2	Feeling down, depressed, or hopeless?	Not at all ☐	Several days ☐	More than half the days ☐	Nearly every day ☐
3	Trouble falling or staying asleep, or sleeping too much?	Not at all ☐	Several days ☐	More than half the days ☐	Nearly every day ☐
4	Feeling tired or having little energy?	Not at all ☐	Several days ☐	More than half the days ☐	Nearly every day ☐
5	Poor appetite or overeating?	Not at all ☐	Several days ☐	More than half the days ☐	Nearly every day ☐
6	Feeling bad about yourself – or that you are a failure or have let yourself or your family down?	Not at all ☐	Several days ☐	More than half the days ☐	Nearly every day ☐
7	Trouble concentrating on things, such as reading the newspaper or watching television?	Not at all ☐	Several days ☐	More than half the days ☐	Nearly every day ☐
8	Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual?	Not at all ☐	Several days ☐	More than half the days ☐	Nearly every day ☐

Appendix B

Cognitive Function Instrument: Self report

Answer all questions with reference to one year ago.				
1	Compared to one year ago, do you feel that your memory has declined substantially?	□ Yes	□ No	□ Maybe
2	Do others tell you that you tend to repeat questions over and over?	□ Yes	□ No	□ Maybe
3	Have you been misplacing things more often?	□ Yes	□ No	□ Maybe
4	Do you find that lately you are relying more on written reminders (e.g., shopping lists, calendars)?	□ Yes	□ No	□ Maybe
5	Do you need more help from others to remember appointments, family occasions or holidays?	□ Yes	□ No	□ Maybe
6	Do you have more trouble recalling names, finding the right word, or completing sentences?	□ Yes	□ No	□ Maybe
7	Do you have more trouble driving (e.g., do you drive more slowly, have more trouble at night, tend to get lost, have accidents)?	□ Yes	□ No	□ Maybe
8	Compared to one year ago, do you have more difficulty managing money (e.g., paying bills, calculating change, completing tax forms)?	□ Yes	□ No	□ Maybe
9	Are you less involved in social activities?	□ Yes	□ No	□ Maybe
10	Has your work performance (paid or volunteer) declined significantly compared to one year ago?	□ Yes	□ No	□ Maybe
11	Do you have more trouble following the news, or the plots of books, movies or TV shows, compared to one year ago?	□ Yes	□ No	□ Maybe
12	Are there any activities (e.g., hobbies, such as card games, crafts) that are substantially more difficult for you now compared to one year ago?	□ Yes	□ No	□ Maybe
13	Are you more likely to become disoriented, or get lost, for example when traveling to another city?	□ Yes	□ No	□ Maybe
14	Do you have more difficulty using household appliances (such as the washing machine, VCR or computer)?	□ Yes	□ No	□ Maybe

Appendix C

EMORY UNIVERSITY | Institutional Review Board

November 1st, 2016

Priscilla Elizabeth Davidson
Rollins School of Public Health

RE: Determination: No IRB Review Required
Title: Association between depression and cognitive function: the Emory Healthy Aging Study
PI: Priscilla Davidson

Dear Priscilla,

Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition of research with "human subjects" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will be receiving questionnaires regarding subjects' responses about depression and cognitive function. These questionnaires will be completely stripped of any HIPAA identifiers.

Please note that this determination does not mean that you cannot publish the results. This determination could be affected by substantive changes in the study design or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for

consulting the

IRB. Sincerely,

Parul Reddy
Analyst Assistant
Emory University Institutional Review Board