ANXIETY SYMPTOMS, ANXIOLYTIC MEDICATIONS AND COGNITIVE IMPAIRMENT IN OLDER ADULTS

by

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ABSTRACT

Worldwide, anxiety disorders are the sixth leading cause of all years of life lived with disability, ahead of diabetes, cancers and stroke. In the United States, anxiety disorders are the most common mental disorders among older adults. It is well documented that anxiety and cognitive impairment co-occur in older adults, however, the nature of this relationship remains unclear. Further, medications that are used to manage anxiety symptoms and disorders appear to be increasing in the general population with paucity of information about trends in older adults. Using three population-based studies, this dissertation investigated anxiety symptoms in older men and women with a focus on anxiety-related medications and impact of anxiety on future cognitive functioning. We found that the use of anxiolytic and antidepressant medications increased in an aging cohort over ten years with higher prevalence in women than men. We also found that some predictors of anxiolytic and antidepressant medications use were common among both men and women, while some predictors were potentially gender-specific. In a cohort of oldest old women, we found that mild anxiety symptoms were associated with increased odds of incident dementia over five years. We also found that change in anxiety symptoms over time was associated with increased risk of dementia. We did not observe an association between anxiety symptoms and mild cognitive impairment. In a cohort of older men, we found that anxiety symptoms were associated with greater declines in both global cognitive function and executive function over three years. We also found that such a decline reached clinically

significant level in executive function but not in global cognitive function. Taken together, these findings are of major public health relevance as they highlight the significance of anxiety symptoms in older adults. Findings from this research will improve our understanding of the role of anxiety as a predictor of future cognitive impairment. It is critical to clarify whether anxiety can early identify those at higher risk or it is a potentially modifiable risk factor. Findings from this research will also inform future intervention research that targets older users of anxiety-related medications.

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1.0 INTRODUCTION

Anxiety disorders refer to mental disorders that are characterized by excessive anxiety and fear and their related disturbances. Anxiety is a mood state associated with anticipation of possible future threat, whereas fear is an emotional response to real or perceived present or imminent threat. Anxiety disorders are distinguished from normal worry and fear by being excessive or persistent. (American Psychiatric Association, 2013)

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), anxiety disorders include the following nine diagnostic entities: separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, panic attack, agoraphobia, generalized anxiety disorder, substance/medication-induced anxiety disorder and anxiety disorder due to another medical condition. These subtypes of anxiety disorders differ from one another in terms of objects or situations that induce anxiety, fear and associated thoughts or beliefs. (American Psychiatric Association, 2013)

It is noteworthy that the DSM-5 classification of anxiety disorders no longer includes obsessive-compulsive disorder, posttraumatic stress disorder or acute stress disorder, which were all classified as anxiety disorders in DSM-IV. (American Psychiatric Association, 2000) Further, anxiety disorders are categorized under the neurotic, stress-related and somatoform disorders chapter of the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

1.1 MEASUREMENT OF ANXIETY

In clinical settings, diagnosis of anxiety disorders is based on the self-report of symptoms by the patient and the determination of whether the symptoms are typical, excessive or persistent by the clinician, while considering the patient's overall health status. (American Psychiatric Association, 2013) In epidemiologic studies, anxiety is assessed using symptom scales or diagnostic schedules. (Murphy, 2011)

Symptom scales assess the presence or absence of interrelated anxiety symptoms and their frequency on a numeric rating scale. (Murphy, 2011) A sum score is produced and a cutoff is used to define cases and non-cases. (Murphy, 2011) Diagnostic schedules assess the presence or absence of distinct anxiety syndromes and produce categorical diagnoses. (Murphy, 2011) Assessments made by diagnostic schedules are more comprehensive and are usually comparable to clinical interviews; however, they take longer time and are more expensive as they are interviewer-administered, which incur additional training costs. (Murphy, 2011) Thus, most epidemiologic investigations utilize symptom scales. (Murphy, 2011)

A recent systematic review identified 91 assessment measures of anxiety that were used in studies with adults aged 65 years and older; however, only 12 of them were identified as the most commonly used tools in the literature (have been used in at least 6 studies). (Therrien & Hunsley, 2012)

These common tools include the following instruments specific to anxiety: State Trait Anxiety Inventory (STAI; 40-item self-report questionnaire) (Spielberger, 1983); Hospital Anxiety and Depression Scale (HADS; 14-item self-report questionnaire) (Zigmond & Snaith, 1983); Hamilton Anxiety Rating Scale (HARS; 14-item clinician-administered rating scale) (Hamilton, 1959); Goldberg Anxiety and Depression Scale (GADS; 18-item self-report

questionnaire) (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988); Beck Anxiety Inventory (BAI; 21-item self-report questionnaire) (Beck, Epstein, Brown, & Steer, 1988); Penn State Worry Questionnaire (PSWQ; 16-item self-report questionnaire) (Meyer, Miller, Metzger, & Borkovec, 1990); Worry Scale (WS; 35-item self-report questionnaire) (Wisocki, Handen, & Morse, 1986), and Geriatric Anxiety Inventory (GAI; 20-item self-report questionnaire) (Pachana et al., 2007)

Other common tools but are not specific to anxiety include Geriatric Mental State Examination (GMSE; semi-structured clinical interview) (Copeland et al., 1976), General Health Questionnaire (GHQ; 60, 30, 28, 20 and 12 items self-report questionnaires) (Goldberg, 1978), Brief Symptom Inventory (BSI, 53-item self-report questionnaire) (Derogatis & Spencer, 1982), and Symptom Checklist 90-R (SCL-90-R; 90-item self-report questionnaire). (Derogatis, 1994)

The large majority of these common measures of anxiety were created for use in younger adults and there is lack of psychometric evidence to support their use in older adults. (Therrien & Hunsley, 2012) Of the 12 common measures, 3 measures were developed specifically for older adults (GAI, GMSE, WS), and 3 measures had sufficient psychometric evidence to warrant their use in older adults (BAI, GMSE, PSWQ). (Therrien & Hunsley, 2012) More recently, the Geriatric Anxiety Scale (GAS; 30-item self-report questionnaire) was developed as a new measure of anxiety for use with older adults. (Segal, June, Payne, Coolidge, & Yochim, 2010)

It is important to highlight that assessment of anxiety in older adults is complicated in several ways. First, strong co-morbidity of anxiety and depression may lead to misclassification if the assessment tool does not adequately differentiate between symptoms of both conditions. (Therrien & Hunsley, 2012) Second, increased frequency of medical conditions in older adults may lead to misclassification if the assessment tool includes high number of somatic symptoms

related to medical conditions that could be attributed by participants or interviewers to anxiety. (Therrien & Hunsley, 2012) Finally, cognitive status and medications use are important considerations when assessing anxiety in older adults as they may alter presentation and communication of anxiety symptoms. (Therrien & Hunsley, 2012)

1.2 EPIDEMIOLOGY OF ANXIETY

Globally, Baxter, Scott, Vos, and Whiteford (2013) conducted a systematic review and meta-regression analyses that included 87 studies from 44 countries to estimate prevalence of anxiety disorders. Adjusted for methodological differences across studies, the authors estimated the global current prevalence of anxiety disorders as 7.3% and it ranged from 5.3% in African countries to 10.4% in countries in Western Europe, North America and Australasia. (Baxter et al., 2013)

In the United States, recent estimates of mental disorders prevalence are based on findings from the National Comorbidity Survey Replication. The National Comorbidity Survey Replication is a nationally representative survey of 9282 non-institutionalized adults aged 18 years and older that utilized DSM-IV criteria to assess mental disorders. (Kessler, Chiu, Demler, Merikangas, & Walters, 2005) According to the National Comorbidity Survey Replication, anxiety disorders are the most common mental disorders in the United States with a lifetime prevalence of 28.8% (Kessler, Berglund, et al., 2005) and 12-month prevalence of 18.1%. (Kessler, Chiu, et al., 2005)

Further analyses from the National Comorbidity Survey Replication showed that anxiety disorders are also common among older adults. The lifetime prevalence of any anxiety disorder

was estimated as 16.6% among women and 9.6% among men aged 65 years and older. (Gum, King-Kallimanis, & Kohn, 2009) In participants aged 55 years and older, the overall 12-month prevalence of anxiety disorders was estimated as 11.6% with the following age-specific estimates: 16.6% for 55-64 years group; 8.9% for 65-74 years group; 6.0% for 75-84 years group and 8.1% for ≥ 85 years group. (Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010) The study reported that 14.7% of older women and 7.6% of older men had at least one anxiety disorder in the past year and that there were no differences in prevalence by race or ethnicity. (Byers et al., 2010) The National Epidemiologic Survey on Alcohol and Related Conditions, another nationally representative survey in the United States, reported comparable estimates of anxiety disorders prevalence in older adults. (Reynolds, Pietrzak, El-Gabalawy, Mackenzie, & Sareen, 2015)

It is important to note that other studies reported a wide variation in the prevalence estimates of anxiety in older adults. (Bryant, Jackson, & Ames, 2008) In community samples, prevalence of anxiety disorders ranged from 1.2% in a New York sample aged 65-90 years (Copeland et al., 1987) to 14% in a French sample aged 65 years and older (Ritchie et al., 2004), while prevalence of anxiety symptoms ranged from 15% in an American sample aged 70-79 years (Mehta et al., 2003) to 52.3% in a German sample aged 70-103 years. (Schaub & Linden, 2000) In clinical samples, prevalence of anxiety disorders ranged from 1% in an Australian sample aged 65 years and older from a general hospital (Ames & Tuckwell, 1994) to 24% in an American sample aged 50 years and older from a primary care setting (Tolin, Robison, Gaztambide, & Blank, 2005), while prevalence of anxiety symptoms ranged from 15% in an Australian sample aged 61-96 years from a geriatric hospital (Ames et al., 1994) to 56% in an Australian sample aged 65 years and older from a general hospital. (Ames & Tuckwell, 1994)

These discrepant findings are most likely due to methodological differences across studies in terms of source population, age group, measurement tool and definition of anxiety. Nevertheless, current literature indicates that anxiety and its disorder are indeed common in older adults.

Evidence regarding the incidence rates of anxiety in older adults is scarce. Based on analyses from the National Epidemiologic Survey on Alcohol and Related Conditions, Chou, Mackenzie, Liang, and Sareen (2011) reported 3-year incidence rates for anxiety disorders among participants aged 60 years and older that ranged from 0.58% for social phobia to 1.63% for generalized anxiety disorder. The study showed that older women were twice as likely to develop generalized anxiety disorder compared to older men (odds ratio = 2.26). (Chou et al., 2011) Similar gender difference in incidence rate was reported by a study based on a representative sample in the Netherlands. (Bijl et al., 2002) Among participants aged 55-64 years, the incidence rate per 100 person-years of any anxiety disorders was 5.20 for women and 1.36 for men. (Bijl et al., 2002)

Few longitudinal studies examined risk factors for anxiety in older adults. de Beurs, Beekman, Deeg, Van Dyck, and van Tilburg (2000) examined risk factors for change in anxiety symptoms in 2,165 older adults aged 55-85 years from the Longitudinal Aging Study Amsterdam over 3 years. The authors reported the significant independent predictors of becoming anxious, with standardized coefficients from multiple logistic regression models, as follows: female gender (3.60), neuroticism (3.81) and distress (2.68). (de Beurs et al., 2000) Further analyses from the same study, after excluding those with existing anxiety or depression (N=1,810 participants), showed the following significant predictors, along with the corresponding adjusted odds ratio: higher initial anxiety symptoms (1.4), female gender (5.1), less received emotional

support (2.1), poor self-rated health (2.1), neuroticism (2.2) and lower self-efficacy (2.1). Furthermore, illness of the partner, illness or death of a family member, having major conflict, or having been victimized by crime, were all significantly associated with increased risk of anxiety symptoms in multivariate models, however, authors did not report effect size. (de Beurs et al., 2001)

Forsell (2000) studied 894 older adults (mean age = 84.5 years, 77.3% women) in Sweden to explore predictors of anxiety symptoms. The author reported that developing anxiety symptoms at 3-year follow-up was significantly associated with history of depression or anxiety (adjusted odds ratio = 4.5) and having no regular visitors (adjusted odds ratio = 3.5). Schoevers, Deeg, van Tilburg, and Beekman (2005) studied 2,173 older adults aged 65-84 years (63.1% women) from the Amsterdam Study of the Elderly to examine predictors of generalized anxiety disorder over 3 years of follow-up and reported that only personal history of depression or anxiety was a statistically significant predictor (adjusted odds ratio = 2.58). To summarize, it appears from the available evidence that female gender and history of anxiety or depression were the most consistent risk factors for anxiety in older adults.

1.3 PUBLIC HEALTH BURDEN OF ANXIETY

According to the 2010 Global Burden of Disease study, anxiety disorders were the sixth leading cause of all years of life lived with disability (YLD) in both high-income and low- and middle-income countries, ahead of diabetes, cancers and stroke. (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014) The study showed that anxiety disorders accounted for 509 YLDs per 100,000 women and 272 YLDs per 100,000 men worldwide. (Baxter et al., 2014)

In older adults, de Beurs et al. (1999) utilized cross-sectional data of 659 participants aged 55-85 years from the Longitudinal Aging Study Amsterdam and reported that anxiety disorders and symptoms were significantly associated with one or more days when activities were limited due to health problems (versus no days), with adjusted odds ratio of 1.6 (95% confidence interval 1.2, 2.3) for anxiety disorders and 3.2 (95% confidence interval 1.9, 5.3) for anxiety symptoms. Further, Brenes et al. (2005) studied 1,002 disabled older women (average age 78.3 years) from the Women's Health and Aging Study and found that anxiety symptoms were significantly associated with risk of developing another functional disability over 3 years with the following adjusted hazard ratios: 1.41 (95% confidence interval 1.08, 1.84) for difficulty in activities of daily living and 1.56 (95% confidence interval 1.14, 2.14) for difficulty in light housework.

In terms of mortality, additional analyses from the Longitudinal Aging Study Amsterdam sample showed that the mortality rates at 7.5-year follow-up for participants with an anxiety disorder were 105.6 and 38.7 per 1000 person-years for men and women, respectively. (van Hout et al., 2004) The adjusted hazard ratios for mortality for men and women with anxiety disorders in the study were 1.78 and 0.89, respectively, but only were statistically significant for men. (van Hout et al., 2004) Additionally, Brenes et al. (2007) examined this relationship in 3,015 older adults aged 70-79 years from the Health Aging and Body Composition study over 7 years. The authors reported that anxiety symptoms were significantly associated with risk of all-cause mortality in African Americans (adjusted hazard ratio = 2.28) but not in Whites. (Brenes et al., 2007) In conclusion, anxiety in older adults is a significant disabling condition that may increase risk of death.

1.4 TREATMENT OF ANXIETY

Anxiety disorders in older adults are treated with pharmacotherapy or psychotherapy or both combined, (Lenze & Wetherell, 2011) (Hendriks, 2014) The focus of this dissertation is pharmacotherapy. In this dissertation, the term "anxiolytic" broadly refers to medications that are used to manage anxiety symptoms or disorders. Benzodiazepines represent the main class and the most commonly prescribed class among anxiolytic medications. (Lenze & Wetherell, 2011) Several other classes of medications are used to treat anxiety disorders and symptoms including non-benzodiazepine sedative-hypnotics, antidepressants, buspirone, anticonvulsants, antipsychotics and antihistamines, but most of these medications need more evidence to support their use in older adults. (Janicak, Marder, & Pavuluri) Increasing evidence suggests that antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), may be equally effective in older adults as in younger adults, and are now recommended as the first line of treatment for anxiety disorders. (Lenze & Wetherell, 2011) (Hendriks, 2014) Studies in clinical settings of older adults with anxiety disorders have confirmed high rates of benzodiazepine and antidepressant use in this patient population. (Benitez et al., 2008) (Uchida et al., 2009) (Preville et al., 2011)

In terms of pharmacodynamics, benzodiazepines enhance the effect of gamma-aminobutyric acid (GABA), the most abundant inhibitory neurotransmitter in the brain. (Janicak et al., 2010) Based on the catecholamine hypothesis, SSRIs and SNRIs operate to inhibit reuptake of serotonin and norepinephrine into the presynaptic cell, which effectively increase availability of these neurotransmitters to bind to the postsynaptic receptor and potentiate their activity in the brain. (Janicak et al., 2010) In terms of pharmacokinetics, benzodiazepines are

generally classified as short acting or long acting depending on their potency, duration of clinical activity, dependency risk, and withdrawal symptoms. (Janicak et al., 2010) SSRIs vary by their ability to inhibit their cytochrome P450 isoenzyme metabolic activity and their elimination half-lives. (Janicak et al., 2010) It is noteworthy that some studies suggest that oral clearance of benzodiazepines may be higher in women than in men. (Greenblatt et al., 2000) This may lead women to consume benzodiazepines in high dose and frequency to achieve optimal effect.

Older adults are more susceptible to adverse effects of psychotropic medications due to age-related physiological changes altering medication absorption, distribution, metabolism and excretion.(Janicak et al., 2010; Lindsey, 2009) Medical co-morbidity and polypharmacy in older adults also affect pharmacokinetic and pharmacodynamic properties of these medications.(Janicak et al., 2010; Lindsey, 2009)

Benzodiazepines use in older adults has been associated with several adverse outcomes including cognitive decline (Paterniti, Dufouil, & Alperovitch, 2002), hip fracture (Wagner et al., 2004), falls (Landi et al., 2005) and disability. (Gray et al., 2006) Comparable, yet debatable, findings have been observed with antidepressants use as well.(Coupland et al., 2011; Darowski, Chambers, & Chambers, 2009; Gebara et al., 2014) Further, the updated American Geriatrics Society Beers Criteria designated a number of antidepressants along with benzodiazepines as potentially inappropriate medications for use in older adults. (American Geriatrics Society Beers Criteria Update Expert, 2012)

Benzodiazepines and antidepressants are widely used medications in the United States. For instance, dispensed prescriptions for alprazolam, a benzodiazepine medication, have increased from 43.3 million in 2008 to 49.2 million in 2012. (IMSHealth, 2013) Similarly, dispensed prescriptions for citalopram and sertraline, SSRI medications, have increased from

22.6 and 33.7 million in 2008 to 38.9 and 39.2 million in 2012, respectively. (IMSHealth, 2013) Further, clinicians wrote 37.6 benzodiazepine prescriptions per 100-person in 2012. (Paulozzi, Mack, & Hockenberry, 2014)

Few longitudinal studies have explored patterns of anxiolytic medication use specifically in community-dwelling older adults in the United States. Dealberto, Seeman, McAvay, and Berkman (1997) studied 2,812 older adults aged 65 years and older from 1982 to 1988 and reported that benzodiazepines were used by 6.25% of the total sample and their use remained stable over time (5.96% in 1985 to 6.06% in 1988). The authors reported that women were about twice as likely as men to use benzodiazepines (7.65% versus 3.78%, $p < 0.001$). (Dealberto, Seeman, et al., 1997) D. Blazer, C. Hybels, E. Simonsick, and J. T. Hanlon (2000) studied 4,000 community dwelling older adults aged 65 years and older from 1986 to 1996. For benzodiazepines, 12% and 10.2% of participants were users in 1986 and 1996, respectively. (D. Blazer et al., 2000) For non-benzodiazepine sedative-hypnotics, 1.6% and 0.7% of participants were users in 1986 and 1996, respectively. (D. Blazer et al., 2000) The authors reported the statistically significant predictors of sedative, hypnotic, and antianxiety medication use at four visits as follows, with the corresponding adjusted odds ratio for each factor: depressive symptoms (2.13), medical outpatient visits (2.30), female gender (1.87), fair or poor perceived health (2.12), white race (4.70) and impaired physical function (1.64). (D. Blazer et al., 2000) Utilizing the same sample but focusing on antidepressants, Blazer et al. (2000) found that use of these medications increased from 3.8% in 1986-1987 to 11.0% in 1996-1997 and that female gender is a highly significant correlate at baseline but not at follow-up. (D. G. Blazer, C. F. Hybels, E. M. Simonsick, & J. T. Hanlon, 2000) Stowell, Chang, Bilt, Stoehr, and Ganguli (2008) studied 1,342 older adults aged 65 years and older from 1991 to 2002 to examine factors associated with sustained benzodiazepine use at

two consecutive waves. At baseline, 9.8 % of women and 5.5 % of men were benzodiazepines users. (Stowell et al., 2008) The authors reported the statistically significant predictors of sustained benzodiazepine use as follows, with the corresponding adjusted odds ratio for each factor: female gender (2.57), two or more non-benzodiazepine prescription medications (5.20) and ever smoked (3.01). (Stowell et al., 2008) Overall, it appears from the few studies that were conducted that female gender is the most consistent correlate of anxiolytic medication use in older adults.

1.5 COMORBIDITIES OF ANXIETY

Literature documented comorbidity of anxiety in older adults with psychiatric conditions (such as depression, substance use), medical conditions (such as cardiovascular disease, respiratory disease, vestibular problems) and cognitive impairment (such as cognitive decline, severe cognitive impairment). (Wolitzky-Taylor, Castriotta, Lenze, Stanley, & Craske, 2010) (Beaudreau & O'Hara, 2008) The focus of this dissertation is the relationship between anxiety and cognitive impairment in older adults, which will be discussed in the following sections.

1.5.1 Anxiety and cognitive impairment

The focus of this dissertation is the general symptoms of anxiety that are often associated with generalized anxiety disorder. Generalized anxiety disorder is characterized by excessive and persistent anxiety and worry that are hard to control, cause significant distress or impairment and occur on more days than not for at least six months about a number of activities or events.

(AmericanPsychiatricAssociation, 2013) Other features of generalized anxiety disorder include somatic symptoms (being easily fatigued, muscle tension, sleep disturbance), cognitive symptoms (difficulty concentrating or mind going blank) and affective symptoms (irritability, restlessness or feeling keyed up or on edge). (AmericanPsychiatricAssociation, 2013)

There are multiple lines of evidence that suggest an association between anxiety and cognitive impairment in older adults. First, cross-sectional studies documented lower cognitive function in older adults with heightened anxiety. Beaudreau and O'Hara (2009) studied 102 community-dwelling older adults (median age 71 years) and found that elevated anxiety symptoms (measured by the Beck Anxiety Inventory) were significantly associated with poorer inhibition (measured by the Stroop Color and Word Test) and slower processing speed/shifting attention (measured by the Symbol Digit Modality Test). The authors found that elevated anxiety was not associated with episodic memory, semantic memory or word fluency.(Beaudreau & O'Hara, 2009) In another study of 48 community-dwelling older adults (mean age 69 years, 73% women), Stillman, Rowe, Arndt, and Moser (2012) found that anxiety symptoms (measured by the Symptom Checklist-90-Revised) had significant inverse relationship with global cognitive function (measured by the Repeatable Battery for the Assessment of Neuropsychological Status) and its sub-measures of visuospatial ability as well as immediate and delayed memory. The authors reported that anxiety symptoms were not associated with sub-measures of attention or language.(Stillman et al., 2012) Similarly, Yochim, Mueller, and Segal (2013) studied 120 older adults (mean age 74.9 years, 62% women) and reported that anxiety symptoms (measured by the Anxiety Geriatric Anxiety Scale) were significantly associated with reduced performance of immediate verbal memory (measured by California Verbal Learning Test) and executive function (Delis–Kaplan Executive Function System), including categorization and task

switching. In this study, anxiety symptoms were not related to verbal fluency performance.(Yochim et al., 2013)

In a larger sample from the Longitudinal Aging Study Amsterdam, Bierman, Comijs, Jonker, and Beekman (2005) studied 2,615 participants (mean age 70.2 years, 51.1% women) and reported that mild anxiety symptoms (measured by the Hospital Anxiety and Depression Scale) were associated with better cognitive functioning, whereas severe anxiety symptoms were negatively associated with cognitive performance. This curvilinear relationship reached the level of significance for global cognitive function (measured by the Mini-Mental State Exam) and for measures of processing speed (measured by the Coding Task) and episodic memory (measured by the Auditory Verbal Learning Test) but not for fluid intelligence (measured by Raven Progressive Matrices). (Bierman et al., 2005) In another population-based sample, Wetherell, Reynolds, Gatz, and Pedersen (2002) studied 704 older adults (mean age 63.7 years, 59.1% women) from the Swedish Adoption/Twin Study of Aging and found that higher state anxiety (measured by the State Trait Personality Inventory-Anxiety subscale) was associated with poorer performance on tests for vocabulary (measured by the Synonyms test), verbal reasoning (measured by the Analogies test), visuospatial ability (measured by the Koh's Block Design) and visual memory (Names and Faces and Thurstone's Picture Memory). The authors found no significant effects of state anxiety on attention, working memory, visual reasoning and verbal knowledge.(Wetherell et al., 2002) The authors also did not find a curvilinear relationship between state anxiety and cognitive function, but they did find significant interaction between state anxiety and gender on two tests (Card Rotations and Digit Span), in which men performed worse compared to women. (Wetherell et al., 2002) State anxiety refers to temporary emotions and is distinguished from trait anxiety, a personality construct. (Spielberger, 1983)

In another study of state anxiety, Curiel et al. (2012) studied 267 older adults (mean age 61.84 years, 62.9% women) and found that state anxiety (measured by the State Trait Anxiety Inventory) had an inverse relationship with delayed verbal memory (measured by the Wechsler Memory Scale and the Buschke Selective Reminding Test). Finally, Mantella et al. (2007) studied a sample of older adults with generalized anxiety disorder (N=19, mean age 70.2 years, 57.9% women), major depressive disorder (N=68, mean age 71.2 years, 69.1% women) and healthy controls (N=40, mean age 69.9 years, 55% years). Compared to healthy controls, anxious participants performed worse on measures of task switching (measured by the Trail Making Test part B), and short-term and delayed memory (measured by the California Verbal Learning Test). (Mantella et al., 2007)

It is important to note that other studies with conflicting findings do exist. For instance, Airaksinen, Larsson, and Forsell (2005) reported that anxiety disorders as a broad category exhibited impairments in episodic memory and executive functions, but generalized anxiety disorder specifically did not affect cognitive performance. Similarly,Biringer et al. (2005) and Potvin et al. (2013) reported that anxiety had no or positive effect on cognitive function, respectively. Given the cross-sectional design of these studies, it is not possible to determine causality and whether anxiety precedes lower cognitive function or it is a consequence.

Second, cross-sectional studies documented elevated anxiety symptoms in older adults with clinically assessed cognitive impairment. Lyketsos et al. (2002) studied a sample of older adults with mild cognitive impairment (N=320, mean age 75 years, 60% women) and dementia (N=362, mean age 77 years, 63% women) from the Cardiovascular Health Study and compared them to healthy controls (N=653) from the Cache County Study. They found that 21.5% of

dementia participants and 9.9% of mild cognitive impairment participants reported anxiety symptoms (measured by the Neuropsychiatric Inventory) compared to 5.8% of healthy controls. (Lyketsos et al., 2002) The authors reported that the difference in anxiety symptoms between the mild cognitive impairment group and the cognitively normal group was marginally significant but they did not test for difference between the dementia group and the cognitively normal group. (Lyketsos et al., 2002) Lopez et al. (2003) studied 1155 patients (69.8% women) with probable Alzheimer's disease and classified severity of their cognitive deficits using the Mini-Mental State Exam as follows: mild (score of 20 or more), moderate (score between 19 and 10) and severe (score of 9 or less). The authors found that anxiety symptoms (defined according to DSM-IV or DSM-III criteria) were significantly more common among patients with severe deficits (68%) compared to those with mild deficits (60%) or moderate deficits (62%). (Lopez et al., 2003)

Geda et al. (2008) studied participants with mild cognitive impairment (N=319, median age 82 years, 42.6% women) and cognitively intact participants (N=1590, median age 79 years, 50.3% women) from the Mayo Clinic Study of Aging. They found that 14% of mild cognitive impairment participants reported anxiety symptoms (measured by the Neuropsychiatric Inventory Questionnaire) compared to 5% of healthy controls with an adjusted odds ratio of 3.00 (95% confidence interval 2.01, 4.48). (Geda et al., 2008) Potvin, Hudon, Dion, Grenier, and Preville (2011) compared participants with cognitive impairment no dementia (N=234) and cognitively intact participants (N=2180) in terms of anxiety disorders (assessed following DSM-IV criteria). In men, they found that cognitive impairment no dementia was associated with subclinical generalized anxiety disorder with an adjusted odds ratio of 4.93 (95% confidence

interval 1.84, 13.23). However, cognitive impairment no dementia was not related to any clinical or subclinical anxiety disorder in women. (Potvin, Hudon, et al., 2011)

In addition, Andreescu et al. (2014) studied 1,982 older adults (mean age 77.59 years, 61.26% women) with normal or mild cognitive impairment from the Monongahela-Youghiogheny Healthy Aging Team study. Participants were classified according to three definitions of mild cognitive impairment to isolate cognitive and functional deficits, and classified anxiety according to three questions adapted from the Penn State Worry Questionnaire. (Andreescu et al., 2014) The authors found that chronic severe anxiety was significantly associated with mild cognitive impairment by all definitions (with adjusted odds ratios that ranged from 1.52 to 1.80); recent-onset anxiety was significantly associated with mild cognitive impairment by non-amnestic (adjusted odds ratio = 1.94, 95% confidence interval 1.21, 3.11), and International Working Group criteria (adjusted odds ratio = 2.11, 95% confidence interval 1.31, 3.42), and chronic mild worry was not associated with any definition of mild cognitive impairment. (Andreescu et al., 2014) Finally, given the cross-sectional design of these studies, it is not possible to determine causality and whether anxiety is a symptom of cognitive impairment or it precedes it.

Third, two longitudinal studies suggested that anxiety increased the risk of progression of mild cognitive impairment to severe cognitive impairment. Palmer et al. (2007) followed older adults (mean age 84 years, 84.9% women) with mild cognitive impairment (N=47) and normal cognition (N=185) for three years. Compared with 6% of participants with normal cognition, they reported that 83% of participants with both mild cognitive impairment and anxiety symptoms (assessed by the Comprehensive Psychopathological Rating Scale) developed dementia due to Alzheimer's disease (adjusted relative risk = 34.4, 95% confidence interval 13.9,

85.8) while 41% of participants with only mild cognitive impairment developed Alzheimer's dementia (adjusted relative risk = 10.6, 95% confidence interval 4.2, 26.8). (Palmer et al., 2007)

Gallagher et al. (2011) followed 161 patients with mild cognitive impairment (mean age 73.7 years, 43% women) for 27 months and found that anxiety (measured by the Behavioral Pathology in Alzheimer's Disease rating scale) was associated with earlier conversion to Alzheimer's disease (adjusted hazard ratio = 1.85, 95% confidence interval 1.1, 3.1). However, it is important to note that these findings are not universal. Devier et al. (2009) reported that state anxiety did not predict conversion to Alzheimer's disease and that trait anxiety actually predicted lower risk of conversion.

Fourth, there is a strong comorbidity between anxiety and depression, which itself is a potential risk factor for cognitive impairment. (Ganguli, 2009) (Byers & Yaffe, 2011) Based on the National Comorbidity Survey Replication, Kessler et al. (2003) reported that 59.2% and 57.5% of participants with lifetime and 12-month major depressive disorder, respectively, also met criteria for an anxiety disorder. Further analyses from the National Comorbidity Survey Replication revealed that generalized anxiety disorder is strongly correlated with major depressive disorder (r=0.62) and dysthymia (r=0.55). (Kessler, Chiu, et al., 2005) High level of comorbidity was also found in a sample of older adults (mean age = 70.96) in which 47.5% of those with depression also met criteria for anxiety, and 26.1% of those with anxiety also met criteria for depression. (Beekman et al., 2000) To summarize, there is a great overlap between anxiety and depression in older adults in terms of risk profile (Vink, Aartsen, & Schoevers, 2008), presentation and treatment (Lenze, 2003), which may indicate some overlap in the underlying etiology that links these conditions with cognitive impairment.

Fifth, a number of studies reported that use of benzodiazepine, an anxiolytic medication, was associated with risk of cognitive decline or impairment. Four longitudinal studies reported an increased risk for cognitive decline or dementia (Lagnaoui et al. (2002); Paterniti et al. (2002); Gallacher et al. (2012); Billioti de Gage et al. (2012) (Billioti de Gage et al., 2014)), while other longitudinal studies reported no association (Hanlon et al. (1998); Allard, Artero, and Ritchie (2003)) or even lower risk for cognitive impairment (Dealberto, McAvay, Seeman, and Berkman (1997); Fastbom, Forsell, and Winblad (1998)).

In all these studies, only two studies did account for anxiety (Paterniti et al., 2002) (Billioti de Gage et al., 2014), which raises the likelihood of confounding by indication in the reported findings. It is important to note that while the short-term effect of benzodiazepine use on cognition is established (Janicak et al.), the biological plausibility of its long-term effect on cognition is unknown. (Verdoux, Lagnaoui, & Begaud, 2005) Therefore, it is possible that benzodiazepine use could be a marker of an underlying condition, such as anxiety, that led to the reported association with cognitive impairment in several studies.

Sixth, neuroticism, a personality trait characterized by a tendency to respond with negative emotions to stress (Lahey, 2009) and is closely related to anxiety, have been shown by one research group to be associated with cognitive decline (Wilson et al., 2005), mild cognitive impairment Wilson et al. (2007) and Alzheimer's disease. (Wilson et al., 2006) More recently, they found that the anxiety facet of neuroticism was associated with increased risk of Alzheimer's disease and more rapid decline in global cognition in 785 older adults (mean age 80.7 years) over 3.4 years. (Wilson, Begeny, Boyle, Schneider, & Bennett, 2011) However, Wetherell et al. (2002) found no support for neuroticism as a predictor of cognitive decline over

time in cognitively intact 704 older adults (mean age 63.7 years, 59.1% women) from the Swedish Adoption/Twin Study of Aging.

Seventh, there are potential biological mechanisms that may explain the relationship between anxiety disorders and cognitive impairment. The most prominent biological pathway is based on the glucocorticoid-cascade hypothesis of stress and aging. (Sapolsky, Krey, & McEwen, 1986) This pathway postulates that high levels of glucocorticoid hormones result in structural and functional damage to the hippocampus and prefrontal cortex, most notably atrophy, which eventually result in cognitive impairment. (McEwen, 2012) The high levels of glucocorticoid hormones indicate dysfunction in hypothalamic-pituitary-adrenal (HPA) axis, a neuroendocrine mediator of stress. (McEwen, 2012) In response to stress, HPA axis operates in a series of feedback loops starting with the hypothalamus producing corticotropin-releasing hormone (CRH) that stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). Next, ACTH stimulates the adrenal cortex to produce glucocorticoid hormones, mainly cortisol. High cortisol levels regulate CRH and ACTH production via negative feedback. Chronic anxiety may cause HPA axis hyperactivity, which initiates this cascade. (McEwen, 2012) The next potential biological pathway is based on the vascular depression hypothesis, which posits that cerebrovascular disease may predispose, precipitate, or perpetuate depressive symptoms, and subsequently result in cognitive impairment. (Alexopoulos et al., 1997) Given the strong comorbidity between both anxiety and depression, this same pathway may pertain to anxiety as well. Further, some studies found association between anxiety, and cardiovascular disease and diabetes, which provide additional support to this hypothesis in anxiety. (Wolitzky-Taylor et al., 2010) Another potential biological pathway is that individuals with anxiety may have genetic polymorphisms that increase their vulnerability to cognitive impairment at older

age. For instance, short (S) allele of the serotonin transporter-linked polymorphic region (5-HTTLPR), responsible for a reduced level of serotonin in the brain, has been linked to anxiety disorders (Stein, Schork, & Gelernter, 2008) and dementia. (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007) Finally, cellular aging in individuals with anxiety may increase their risk of cognitive impairment at older age. Telomere is a DNA sequence that caps chromosomes and is shortened in subsequent cell divisions. (Sanders & Newman, 2013) Though inconclusive, emerging evidence suggests that a shorter leukocyte telomere length is associated with cognitive function. (Sanders & Newman, 2013) More recently, Shalev et al. (2014) reported that internalizing disorders, such as generalized anxiety disorder, were associated with shorter leukocyte telomere length cross-sectionally and longitudinally over 12 years. In conclusion, there are several biological mechanisms that may potentially explain, jointly or independently, the relationship between anxiety and cognitive impairment; however, more research is needed to better understand these mechanisms.

The above-mentioned multiple lines of evidence are complex and may be interpreted in different ways. First, anxiety could be a consequence of cognitive impairment, as a prodromal symptom of undiagnosed condition causing cognitive impairment, or as a psychological reaction to early cognitive deficits. This prodromal hypothesis can be ruled out by utilizing longitudinal studies in which anxiety is assessed at baseline in a cognitively intact sample. Next, association between anxiety and cognitive impairment could be confounded by shared risk factors, such as depression. This interpretation can be ruled out via statistical adjustment for potential confounding factors, with the assumption that the measured variable is valid, or possibly by excluding participants with these factors.

Finally, anxiety could be a cause or risk factor for cognitive impairment. Anxiety may be implicated in the causal pathway leading to cognitive impairment, directly via patho-physiological mechanisms, or indirectly via behavioral risk factors that drive patho-physiological mechanisms. The etiological hypothesis can be confirmed by utilizing longitudinal studies in which bias and confounding are minimized and potential biological and behavioral mediators can be tested. To conclude, longitudinal research is critical in interpreting the above-mentioned multiple lines of evidence and in understanding the complex relationship between anxiety and cognitive impairment in older adults.

1.5.2 Longitudinal research on anxiety and cognitive impairment

In total, 12 longitudinal studies investigated whether anxiety in cognitively normal older adults predicted incident cognitive impairment or decline. (Appendix A)

In terms of study design, two studies had a case-control design (Burton, Campbell, Jordan, Strauss, and Mallen (2013) (Zilkens, Bruce, Duke, Spilsbury, & Semmens, 2014), while all the other studies had a prospective cohort design. All the studies were conducted in high-income countries with four studies conducted in Australia, two studies conducted in each of the Netherlands, the United Kingdom and the United States, and one study conducted in each of Canada and Israel. Sample size in the studies ranged from 137 in the study by Sinoff and Werner (2003) to 16,351 in the study by Okereke and Grodstein (2013), but the majority of the studies had sample sizes exceeding one thousand participants.

All studies comprised community-dwelling older adults except for three studies as follows: Sinoff and Werner (2003) studied individuals who were referred to a geriatric assessment unit, Burton et al. (2013) studied patients registered in 10 primary care practices, and

Zilkens et al. (2014) utilized administrative health records. All samples included men and women except for the study by Gallacher et al. (2009) that included only men and the study by Okereke and Grodstein (2013) that included only women. The average age in the studies was in the sixties and seventies except for two studies as follows: Burton et al. (2013) studied cases and controls with a mean age of 81.40 and 80.87 years, respectively and Gallacher et al. (2009) studied men with a mean age of 56.1 years. The follow-up duration in the prospective cohort studies ranged from 1 to 17 years with about half of the studies with a follow-up duration of 4 years or less. In two studies, participants with more anxiety symptoms and lower cognitive performance had higher dropout rates from the study. (Bierman, Comijs, Rijmen, Jonker, & Beekman, 2008) Gallacher et al. (2009)

The large majority of the studies assessed anxiety symptoms and two of the studies assessed anxiety disorders in addition to symptoms. (Potvin, Forget, Grenier, Preville, & Hudon, 2011) (de Bruijn et al. (2014) One study assessed pathologic worry specifically (Pietrzak et al., 2012), one study assessed phobic anxiety symptoms specifically (Okereke and Grodstein, 2013), and one study utilized informant-report measure to assess anxiety. (Geda et al., 2014) With the exception of one study (Bierman et al., 2008), anxiety was analyzed as a categorical exposure variable indicating the presence or absence of anxiety symptoms or disorders in all studies.

To assess cognitive impairment, six studies utilized cognitive function tests and six studies utilized clinical adjudication. Two of the studies that used cognitive testing had a cutoff to define a dichotomous variable for cognitive impairment (Sinoff and Werner (2003) (Potvin, Forget, et al., 2011), while the other four predicted decline in cognitive function as a continuous variable. Bierman et al. (2008) Pietrzak et al. (2012) (Okereke and Grodstein, 2013) (Pietrzak et al., 2015) The studies that utilized clinical adjudication either assessed mild (Cherbuin et al.,

2009) (Geda et al., 2014) or severe (Burton, Campbell, Jordan, Strauss, and Mallen (2013) de Bruijn et al. (2014) cognitive impairment, with only one study that assessed both levels of cognitive impairment. Gallacher et al. (2009) de Bruijn et al. (2014) also assessed cognitive decline. However, none of the studies comprehensively assessed decline in specific cognitive tests and both levels of clinically assessed cognitive impairment (mild cognitive impairment and dementia).

Two studies did not adjust for depression (Gallacher et al. (2009) (Geda et al., 2014) and three of the studies did not account for cardiovascular diseases or other chronic medical conditions. (Sinoff and Werner (2003) Pietrzak et al. (2012) de Bruijn et al. (2014) Only three studies adjusted for psychotropic medication use. Bierman, Comijs, Rijmen, Jonker, and Beekman (2008) Cherbuin et al. (2009) (Potvin, Forget, et al., 2011) All these factors are known to be associated with anxiety and cognitive impairment and thus are potential confounding factors that need to be taken into account. (Wolitzky-Taylor et al., 2010) (Beaudreau & O'Hara, 2008)

In total, eight studies reported that anxiety significantly predicted increased cognitive impairment or decline while four studies found no association. In the studies that reported positive association between anxiety and cognitive impairment or decline, the effect size ranged from an adjusted hazard ratio of 1.87 reported by Geda et al. (2014) to an adjusted odds ratio of 6.27 reported by Potvin, Forget, et al. (2011). Two of the studies reported gender differences in which anxiety had smaller effect (Potvin, Forget, et al., 2011) or no effect (Burton et al., 2013) in women compared to men.

Several methodological limitations may explain the contradictory findings reported by the longitudinal studies that investigated the association between anxiety and subsequent

cognitive impairment in older adults. The studies utilized diverse samples with different age structure. It is possible that the risk profile for cognitive impairment within the source populations in these studies is not similar. It is also likely that the association between anxiety and cognitive impairment varies by the age group.

In terms of exposure assessment, there was a wide variation across studies regarding anxiety measurement tools and definitions. Anxiety in most of these studies was not assessed clinically. Relying on self-report or informant-report symptom scales or medical records rather than objective assessments may have led to misclassification. Outcome definitions were heterogeneous as well and many studies relied on cognitive function tests without clinical judgment. This also may have led to misclassification.

Furthermore, studies varied considerably in their consideration of potential confounding factors such as depression, psychotropic medications and chronic medical conditions. This may have distorted the reported findings and made it difficult to disentangle the effect of anxiety. In addition, losses to follow-up in two studies were associated with anxiety and cognitive impairment, which may have biased the results. About half of the studies had follow-up duration of four years or less. Cognitive impairment is a degenerative condition with a long prodromal period during which prodromal anxiety symptoms may appear before a formal diagnosis is established. Therefore, it is important to have long follow-up duration to ensure that participants at the baseline are truly cognitively intact. In summary, more studies addressing these limitations are needed in order to clearly understand the relationship between anxiety and subsequent cognitive impairment in older adults.

The literature that examined the longitudinal relationship between anxiety and cognitive impairment in older adults has a number of gaps. First, only two studies, one based on informant-

reported anxiety and one based on phobic anxiety, were conducted in the United States and this limits the generalizability of findings to this country. Second, no prospective cohort studies were conducted in the oldest old (80 years and older) population that may have different characteristics leading to their survival to this old age. Therefore it is important to examine how anxiety predicts future cognitive functioning in this unique population.

Third, there were no prospective cohort studies that investigated how characteristics of anxiety are related to cognitive impairment. Variables such as number of anxiety symptoms, specific symptoms of anxiety and change in anxiety over time are important unexplored characteristics that may shed light on the complex relationship between anxiety and cognitive impairment. Fourth, none of the studies examined the effect of anxiety across the full cognitive spectrum, which spans cognitive decline, mild cognitive impairment and severe cognitive impairment. This is particularly important to identify possible trends in the relationship between anxiety and cognitive impairment and to facilitate comparison of findings across studies. Fifth, many previous studies did not account for critical potential confounding factors such as depression, psychotropic medications and chronic medical conditions.

2.0 SPECIFIC AIMS

2.1 ANXIOLYTIC MEDICATIONS USE IN OLDER ADULTS

In the general population, use of medications that are used to manage anxiety symptoms and disorders appears to be increasing. However, it remains unknown whether these recent trends are similar in older adults. Most of the longitudinal community-based studies that examined anxiolytic medications in older adults were conducted in the 1980s and 1990s. Given the serious adverse effects of these medications in older adults, it is important to examine trends of their use in more recent years and to understand the profile of their users in the community. Further, literature showed that female gender is the most consistent correlate for anxiolytic medications use with higher prevalence among women than men. Gender-specific predictors of use of these medications remain unclear and understudied. Since women have greater life expectancy and represent a larger proportion of older adults, it is crucial to understand the socio-demographic and health-related predictors of their use of anxiolytic medications. Understanding patterns and correlates of anxiolytic medications use over time will inform future programs that aim to reduce inappropriate use of medications in older adults.

2.1.1 Specific Aim 1

We aim to investigate the trend of anxiolytic and antidepressant medications use, and to investigate gender-specific predictors of use of these medications over time among older community-dwelling men and women in the Health, Aging and Body Composition Study.

2.2 ANXIETY AND COGNITIVE IMPAIRMENT IN OLDER ADULTS

The longitudinal relationship between anxiety symptoms and subsequent cognitive impairment in older adults remains unclear. Previous research examining this relationship has reported contradictory findings, and was limited by small sample size, short follow-up, not accounting for important confounders and measurement issues. Previous longitudinal studies also did not investigate the role of specific characteristics of anxiety symptoms in relation to cognitive impairment. Further, it is important to explore the relationship between anxiety symptoms and cognitive impairment separately for each gender. Female gender is the most consistent correlate and risk factor for anxiety symptoms and disorders. Women with anxiety have higher disability compared to men and men with anxiety have higher mortality compared to women. These findings may reflect unique pathophysiological profiles in men and women due to biological, environmental or cultural differences. Finally, it is important to disentangle the independent influence of anxiety on cognitive impairment from depression, given their strong comorbidity. Addressing present gaps in literature will help in understanding the role of anxiety as a predictor of future cognitive impairment and whether anxiety is a potentially modifiable risk factor or can early identify those at higher risk. Findings will direct future studies that aim to explore potential mechanisms underlying both conditions that are specific to older men or older women.

2.2.1 Specific Aim 2

We aim to investigate the relationship between presence, level and changes of anxiety symptoms, and risk of future dementia, MCI and decline in cognitive functioning among the oldest old community-dwelling women in the Study of Osteoporotic Fractures.

2.2.2 Specific Aim 3

We aim to investigate the relationship between presence and level of anxiety symptoms, and risk of future cognitive decline among older community-dwelling men in the Osteoporotic Fractures in Men Study.

3.0 PAPER 1: TRENDS AND GENDER-SPECIFIC PREDICTORS OF ANXIOLYTIC AND ANTIDEPRESSANT MEDICATIONS USE IN OLDER ADULTS

3.1 ABSTRACT

Background: Recent research investigating use of anxiolytic or antidepressant medications in older adults is limited. We examined the prevalence and trend of anxiolytic and antidepressant medications use in older adults and explored gender-specific predictors of their use over time. **Methods:** We studied 3,055 older community-dwelling adults (mean age = 73.63, SD ±2.87 years) who were followed on average for 10.29 years. Medications were collected at 3 clinic visits and coded using the Iowa Drug Information Service scheme. We assessed a series of demographic, health status, life style and healthcare covariates. We used logistic regression models with generalized estimating equations to identify gender-specific predictors of anxiolytic and antidepressant medications use over time. **Results:** At baseline, 202 (6.61%) women used anxiolytic or antidepressant medications compared to 110 (3.60%) men. Use of these medications increased from 10.21% in 1997-1998 to 16.82% in 2007-2008. Caucasian race was an independent predictor of both anxiolytic and antidepressant medications use in both men and women. In men, independent predictors of medications use included 3 or more co-morbid medical conditions, getting influenza vaccine and poor/fair self-rated health. In women, independent predictors of medications use included a family income of $25,000 or less, anxiety

and depression. **Conclusion:** Our findings suggest that use of anxiolytic and antidepressant medications increased in this aging cohort and may have gender-specific predictors. Future studies should focus on prescribers to clarify whether the increasing trend in these medications is clinically indicated or reflects inappropriate use.

3.2 INTRODUCTION

Anxiety disorders are the most prevalent mental health problems.(Kessler, Berglund, et al., 2005) Both anxiolytic and antidepressant medications are used to pharmacologically manage anxiety disorders.(Koen & Stein, 2011) In the United States, use of anxiolytic and antidepressant medications appears to be increasing in the general population.(Mojtabai & Olfson, 2014; Olfson, King, & Schoenbaum, 2015) For instance, dispensed prescriptions for alprazolam, an anxiolytic medication, have increased from 43.3 million in 2008 to 49.2 million in 2012.(IMSHealth, 2013) Similarly, dispensed prescriptions for citalopram and sertraline, antidepressant medications, have increased from 22.6 and 33.7 million in 2008 to 38.9 and 39.2 million in 2012, respectively.(IMSHealth, 2013) However, it remains unknown whether these recent trends are similar in older members of the general population. Most of the longitudinal community-based studies that examined anxiolytic or antidepressant medications use in older adults were conducted in the 1980s and 1990s.(D. G. Blazer et al., 2000; D. Blazer et al., 2000; Dealberto, Seeman, et al., 1997; Stowell et al., 2008)

Older adults are more susceptible to adverse effects of psychotropic medications due to age-related physiological changes altering medication absorption, distribution, metabolism and excretion.(Janicak et al., 2010; Lindsey, 2009) Medical co-morbidity and polypharmacy in older adults also affect pharmacokinetic and pharmacodynamic properties of these medications.(Janicak et al., 2010; Lindsey, 2009) Use of benzodiazepine, a major anxiolytic class, in older adults has been associated with serious adverse outcomes including cognitive decline, hip fracture, falls and disability.(Gray et al., 2006; Landi et al., 2005; Paterniti et al.,

2002; Wagner et al., 2004) Comparable, yet debatable, findings have been observed with antidepressants use as well.(Coupland et al., 2011; Darowski et al., 2009; Gebara et al., 2014) The updated American Geriatrics Society Beers Criteria designated several antidepressants along with benzodiazepines as potentially inappropriate medications for use in older adults due to their unfavorable risk-benefit ratio.(American Geriatrics Society Beers Criteria Update Expert, 2012)

Due to increased vulnerability and potential for inappropriate use, it is important to examine trends of anxiolytic and antidepressant medications use by older adults in more recent years. To inform possible interventions, it is also important to understand the profile of anxiolytic and antidepressant medications users in the community and to explore such profile separately for men and women. Literature shows that gender is the most consistent correlate of anxiolytic and antidepressant medications use, with higher prevalence among women than men(D. G. Blazer et al., 2000; D. Blazer et al., 2000; Dealberto, Seeman, et al., 1997; Stowell et al., 2008). While reasons for such disparity remain unclear and understudied(Voyer, Cohen, Lauzon, & Collin, 2004), it may reflect unique characteristics of men and women due to biological, environmental or cultural differences.

In this longitudinal study, we assessed the prevalence and trend of anxiolytic and antidepressant medications use in older community-dwelling adults over ten years and examined predictors of anxiolytic and antidepressant medications use in both men and women over time. We hypothesized that older adults will exhibit increasing use of anxiolytics and antidepressants over time and that men and women will have different predictors of their anxiolytics and antidepressants use.

3.3 METHODS

3.3.1 Population

We utilized data from the Health, Aging, and Body Composition (Health ABC) study, a prospective cohort study of community-dwelling older adults aged 70 to 79 years.(Newman et al., 2003) In brief, 3,075 African-American and Caucasian men and women were recruited during 1997-1998 from Pittsburgh, Pennsylvania and Memphis, Tennessee using Medicare beneficiary lists. Subjects were not enrolled in Health ABC if they had difficulty carrying out basic activities of daily living, walking quarter of a mile, or climbing ten steps without resting. The institutional review board at each site approved the study and participants provided written informed consent.

For this analysis, we used data collected at baseline (1997-1998), year 6 (2002-2003), and year 11 (2007-2008). Our analytical sample included 3,055 participants as 20 participants had incomplete medication use information at baseline.

3.3.2 Measurement of medication use

At clinic visits, participants were asked to bring all prescription and over-the-counter medications they had taken in the past two weeks. Medications were coded and categorized using the Iowa Drug Information Service (IDIS) scheme.(Pahor et al., 1994) At year 11, non-prescription medications were no longer collected and the period of time during which the medication was last used was changed from two weeks to 30 days. The dependent variables were use versus no use of anxiolytic and antidepressant medications at baseline, year 6 and year 11.

Anxiolytic medications included the following classes with their respective medications(Hendriks, 2014; Lenze & Wetherell, 2011): benzodiazepine anxiolytics [BZDs] (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam and oxazepam); and non-benzodiazepine anxiolytics [NBZDs] (buspirone, butabarbital, hydroxyzine, meprobamate and pregabalin). Antidepressant medications included the following classes with their respective medications: selective serotonin norepinephrine reuptake inhibitors [SNRIs] (desvenlafaxine, duloxetine, milnacipran and venlafaxine); selective serotonin reuptake inhibitors [SSRIs] (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline); and tricyclic antidepressants [TCAs] (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine).

3.3.3 Measurement of covariates

Participant baseline characteristics included the following categories: socio-demographic, health-related, life style and healthcare. Socio-demographic factors included gender, age, race (African-American versus Caucasian), education (less than high school versus high school or higher), marital status (married versus widowed, divorced, separated or never married), annual family income ($25,000 or less versus more than $25,000), and study site.

Health-related factors included self-rated health status (poor or fair versus good, very good or excellent), functional limitation due to hearing problems, functional limitation due to vision problems and body mass index (BMI). Self-reports of physician's diagnoses of select medical conditions were summed to create a co-morbidity index (three or more versus two or less). Medical conditions included stroke, Parkinson's disease, myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, diabetes, hypertension, arthritis and cancer.

Bodily pain in the past 30 days (any versus none) was assessed. Functional status was assessed by collecting information on limitation (any versus none) with five instrumental activities of daily living (IADL), which included walking two to three blocks on level ground, climbing up to ten steps, preparing meals, doing heavy housework, and shopping for groceries.

Poor sleep was defined as frequently not getting enough sleep or feeling sleepy during the day.(Mehta et al., 2003) Anxiety was defined as a positive response (Yes) to at least two of the three items from the anxiety subscale of the Hopkins Symptom Checklist.(Wright et al., 2009) The three items were: 1) During the past week, have you felt nervous or shaky inside; 2) During the past week, have you felt tense or keyed up; and 3) During the past week, have you felt fearful. Depression was defined as a score of 16 or more on the Center for Epidemiologic Studies - Depression (CES-D) scale.(Radloff, 1977) Cognitive function was assessed using Teng's Modified Mini-Mental State (3MS) exam (score 0-100).(Teng & Chui, 1987)

Life style factors included smoking (current, former, never) and alcohol use (current, former, never). Healthcare factors included having a primary care provider, having supplemental health insurance for prescription medications and getting influenza vaccine in the past year.

3.3.4 Statistical analysis

We calculated descriptive statistics for all variables and compared baseline characteristics of users and non-users of anxiolytic and antidepressant medications stratified by gender. For these comparisons, we used chi-squared test for categorical variables (or Fisher's exact test for low expected cell counts), the two-sample t-test for normally distributed continuous variables and the Wilcoxon rank-sum test for skewed continuous variables. Next, we calculated the frequency of anxiolytic and antidepressant medications use for each interview wave stratified by gender and

we tested for trend of medication use over time using Wald tests. Finally, we examined the predictors of anxiolytic and antidepressant medications use over time using logistic regression models with generalized estimating equations (GEE) to account for within-subject correlations. We used unstructured correlation structure and we modeled Time as continuous variable indicating years from baseline. We fit the models in the full sample and we included product terms of gender by each variable to test for interaction. We additionally fit the models for men and women separately. Marital status, self-rated health, anxiety, depression, 3MS score, smoking and alcohol use were entered as time-varying variables. We assessed each variable in univariable models and then we fit multivariable model in which all variables were entered together and the model was progressively reduced until all predictors were significant at $p < 0.05$. Clinic site was enforced in all the multivariable models. All statistical analyses were conducted with Stata version 13.1 (StataCorp LP, College Station, TX, USA).

3.4 RESULTS

Participants were followed on average for 10.29 years (standard deviation [SD] ±0.12). By year 6, a total of 377 participants died, 75 participants were lost to follow-up and 88 participants did not have medication use data, leaving 2,515 participants with complete data for this interview wave. By year 11, a total of 557 participants died, 114 lost to follow-up and 507 did not have medication use data, leaving 1,337 participants with complete data for this interview wave.

3.4.1 Characteristics of participants

Baseline characteristics of users and non-users of anxiolytic medications stratified by gender are presented in Table 3.6.1. Among men, users of anxiolytic medications were more likely to be Caucasian, married, have poor or fair self-rated health, three or more co-morbid medical conditions, IADL limitations, anxiety and having primary care providers. Among women, users of anxiolytic medications were more likely to have family income of $25,000 or less, limitations due to hearing problems, IADL limitations, bodily pain, poor sleep, anxiety and depression.

Baseline characteristics of users and non-users of antidepressant medications stratified by gender are presented in Table 3.6.2. Among men, users of antidepressant medications were more likely to have poor or fair self-rated health, IADL limitations, anxiety and have received influenza vaccine in the past year. Among women, users of anxiolytic antidepressant were more likely to be Caucasian, have completed high school or higher education, have limitations due to hearing problems, IADL limitations, poor sleep, anxiety and depression.

3.4.2 Trends of anxiolytic and antidepressant medications use

Table 3.6.3 presents the proportion of anxiolytic and antidepressant medications users by gender for each interview wave. At baseline, 202 (6.61%) women used anxiolytic or antidepressant medications compared to 110 (3.60%) men. This gap in use between men and women remained at year 6 and year 11 with higher prevalence of medication use in women than in men. This pattern was also consistent across classes of medications except for SNRIs, which were used by more men than women at baseline and at year 6. Table 2 also shows a statistically significant increasing trend in use of medications in both men and women. This increasing trend was apparent in use of BZDs, SNRIs and SSRIs in both men and women. There was a decreasing trend of TCAs use in men only. There was no consistent trend in use of NBZDs among either men or women.

3.4.3 Predictors of anxiolytic and antidepressant medications use in the full sample

Findings from the GEE logistic regression models for anxiolytics and antidepressants are presented in Table 3.6.4. In unadjusted models, significant predictors of anxiolytic medications use over time were female gender, Caucasian race, poor/fair self-rated health, greater medical co-morbidity, IADL limitations, bodily pain, anxiety and having a primary care provider. In the multivariable model, race, family income, medical co-morbidity, IADL limitations, anxiety and having a primary care provider were significant independent predictors of anxiolytics use. For antidepressants, significant predictors over time were female gender, Caucasian race, poor/fair self-rated health, 3 or more co-morbid medical conditions, IADL limitations, bodily pain, poor sleep, anxiety, depression, having a primary care provider and taking influenza vaccine in the

past year. In the multivariable model, gender, race, IADL limitations, anxiety and depression remained significant independent predictors of antidepressants use. In the models for anxiolytics, only the interaction term of gender by marital status was statistically significant (p=0.01). In the models for antidepressants, only the interaction terms of gender by limitation due to hearing problems, smoking status and BMI were marginally significant (p<0.10).

3.4.4 Predictors of anxiolytic medications use by gender

Findings from the GEE logistic regression models for BZDs and NBZDs are presented in Table 3.6.5. In unadjusted models, among men, significant predictors of anxiolytic medications use over time were Caucasian race, being married, poor/fair self-rated health, greater medical co-morbidity, IADL limitations, anxiety and smoking status (Wald (2) = 6.52, p-value = 0.04). In the multivariable model, only race, self-rated health, medical co-morbidity and anxiety remained significant independent predictors. In women, significant predictors of anxiolytic medications use over time were Caucasian race, poor/fair self-rated health, IADL limitations, bodily pain, anxiety and depression. In the multivariable model, Caucasian race, low family income and anxiety were significant independent predictors.

3.4.5 Predictors of antidepressant medications use by gender

Findings from the GEE logistic regression models for SNRIs, SSRIs and TCAs are presented in Table 3.6.6. In men, significant predictors of antidepressant medications use over time were Caucasian race, having high family income, poor/fair self-rated health, anxiety, depression, a primary care provider and receiving influenza vaccine. In the multivariable model, race, self-

rated health, IADL limitations and influenza vaccine were significant independent predictors. In women, significant predictors of antidepressant medications use over time were Caucasian race, having limitation due to hearing problems, IADL limitations, bodily pain, poor sleep, anxiety, depression, and receiving influenza vaccine. Only race, IADL limitations, anxiety and depression remained significant predictors in the multivariable model for women.

3.5 DISCUSSION

This longitudinal study showed that the use of anxiolytic and antidepressant medications in community-dwelling older adults increased from 10.21% in 1997-1998 to 16.82% in 2007-2008, with higher levels in women than men. For both classes of medications, Caucasian race, any IADL limitations and anxiety were independent predictors of use over time. In men, independent predictors included 3 or more co-morbid medical conditions for anxiolytics use, getting influenza vaccine for antidepressants use and poor/fair self-rated health for use of both medication classes. In women, independent predictors included a family income of $25,000 or less for anxiolytics use, and anxiety and depression for antidepressants use.

Our findings are consistent with one longitudinal community-based study that reported increasing trend in use of SSRIs and TCAs from 1986-1987 to 1996-1997.(D. G. Blazer et al., 2000) However, data from that same sample showed reduction in benzodiazepine use from 12% to 10.2% over ten years of follow-up.(D. Blazer et al., 2000) Another longitudinal community-based study showed that benzodiazepine use remained stable between 1982 and 1988.(Dealberto, Seeman, et al., 1997) Our study presents more recent information on the trend of anxiolytic medication use in community-dwelling older adults. Our findings regarding significant predictors of anxiolytic and antidepressant medications use in community-dwelling older adults are consistent with these longitudinal studies in terms of Caucasian race, depression and self-rated health, but not regarding greater medical co-morbidity. Our study extends this evidence to include anxiety, functional limitation and family income, and identifies which predictors that are potentially gender-specific.

Several consumer and care provider factors may explain the observed increase in use of anxiolytic and antidepressant medications in older adults.(Mojtabai & Olfson, 2014; Olfson et al., 2015) Consumer factors may include increased rate of mental health problems that might have necessitated prescription; change of attitudes toward mental health problems that might have increased healthcare seeking for previously underreported mental health problems; and advertising of psychotropic medications that might have increased requests for prescriptions. Provider factors may include improved detection and diagnosis of mental health problems that might have increased prescribing; limited access or unavailability of alternative effective evidence based treatments, such as psychotherapy, that might have necessitated pharmacotherapy as the sole option; and lack of specialized knowledge regarding risk-benefit ratio of medication use in older adults that might have resulted in increased inappropriate prescribing. However, we cannot confirm the impact of these factors, if any, as we did not measure them. It is important to note that a nationally representative survey reported that mood and anxiety disorders declined with age (Byers et al., 2010), which may indicate that true increase of these mental health problems over time is unlikely. In our sample, prevalence of potential indications, such as anxiety and depression, was generally higher than prevalence of anxiolytic and antidepressant medication use, which may point toward existing but undertreated problems. However, such conclusion should take into account that anxiety and depression were not clinically assessed in our study.

Various hypotheses may explain the different level of psychotropic medication use between men and women.(Voyer et al., 2004) Most of these hypotheses pertain to women and include: women are more likely to report their psychological problems, request prescriptions explicitly, and hold positive views about psychotropic medications. In men, preferring alcohol

use to deal with psychological problems is one hypothesis. We could only directly explore the alcohol-medicating hypothesis, as we did not measure the other factors pertaining to women. In our study, some predictors of anxiolytic and antidepressant medications use were significant in one gender and not the other. While statistical tests for gender differences were not significant, these findings may potentially indicate different healthcare seeking behavior for men and women. Men may not directly seek treatment for their mental health problems, but rather get anxiolytic or antidepressant medications while under care for other issues (as denoted by factors such as medical co-morbidity and getting influenza vaccine). Women may be more explicit about their mental health problems and request treatment with anxiolytic or antidepressant medications (as denoted by factors such as anxiety and depression). However, this explanation is likely speculative and needs confirmation by future studies.

Strengths of this study include the longitudinal design over ten years of follow-up, a large, well-characterized cohort of older community-dwelling adults, and medication data collection that is based on actual medication use by participants rather than medical, pharmacy or administrative records. This study has several limitations. First, the sample included relatively healthy older adults living in two states in the United States and, therefore, may not be representative of other population groups elsewhere. Second, we did not assess the clinical reasons for which these medications were prescribed; however, we measured several potential indications such as anxiety, depression, sleep problems and pain. Third, we did not have data on characteristics of primary care providers including prescribing behavior, which are important factors for medication use.

Our findings suggest that the use of anxiolytic and antidepressant medications is increasing in community-dwelling older adults and may have gender-specific predictors. Future

studies should investigate the risk-benefit ratio for using these medications in the oldest old men and women. Future studies, particularly related to prescribing practices and provider education, should explore potential gender differences in the healthcare seeking behavior in the oldest old.

3.6 TABLES

Table 3.1 Baseline characteristics of users and non-users of anxiolytic medications by gender

Characteristics	Total N = 3,055	Men N = 1,481			Women N = 1,574		
		Non-users N = 1,416	Users N = 65	p-value	Non-users N = 1,466	Users N = 108	p-value
Demographics							
Age (years), mean ± SD	73.63 ± 2.87	73.76 ± 2.88	73.91 ± 2.73	0.7	73.54 ± 2.88	73.05 ± 2.75	0.09
Race (African-American), n (%)	1,266 (41.44)	527 (37.22)	16 (24.62)	0.04	681 (46.45)	42 (38.89)	0.13
Education (less than high school), n (%)	766 (25.14)	384 (27.16)	18 (27.69)	0.9	335 (22.95)	29 (26.85)	0.4
Marital status (married), n (%)	1,568 (54.81)	972 (72.38)	53 (85.48)	0.02	510 (37.61)	33 (33.00)	0.4
Family income ($25,000 or less), n (%)	1,402 (52.24)	550 (42.97)	26 (44.07)	0.9	757 (60.56)	69 (72.63)	0.02
Clinic site (Pittsburgh), n (%)	1,516 (49.62)	715 (50.49)	21 (32.31)	0.004	732 (49.93)	48 (44.44)	0.3
Health status							
Self-rated health (poor/fair), n (%)	493 (16.16)	220 (15.55)	23 (35.38)	<0.001	227 (15.52)	23 (21.30)	0.1
Co-morbid medical conditions (3 or more), n (%)	520 (18.20)	239 (18.16)	22 (37.29)	<0.001	237 (17.15)	22 (22.00)	0.2
Limitation due to hearing problems, n (%)	269 (8.88)	173 (12.33)	8 (12.31)	1.0	76 (5.23)	12 (11.21)	0.01
Limitation due to vision problems, n (%)	268 (8.79)	137 (9.70	2 (3.08)	0.08	118 (8.05)	11 (10.19)	0.4
IADL limitations (any), n (%)	372 (14.63)	94 (8.30)	10 (18.52)	0.01	240 (19.00)	28 (29.79)	0.01
BMI, mean ± SD	27.40 ± 4.82	27.11 3.98	26.24 3.46	0.08	27.75 5.53	27.15 4.97	0.3
Any bodily pain, n (%)	1,999 (65.50)	842 (59.55)	46 (70.77)	0.07	1,020 (69.62)	91 (84.26)	<0.01
Poor sleep, n (%)	344 (11.33)	142 (10.06)	7 (10.77)	0.9	174 (11.99)	21 (19.44)	0.02
Anxiety, n (%)	430 (14.18)	149 (10.58)	15 (23.08)	0.002	222 (15.29)	44 (41.12)	<0.001
Depression, n (%)	144 (4.75)	51 (3.63)	5 (7.81)	0.09	72 (4.95)	16 (14.95)	<0.001
3MS (score), mean ± SD	90.07 ± 8.40	89.57 ± 8.56	88.32 ± 10.60	0.6	90.64 ± 8.15	89.88 ± 7.63	0.2
Life style							

Table 3.1 Continued

Smoking status, n (%)				0.2			0.6
Current	316 (10.36)	153 (10.83)	6 (9.23)		147 (10.04)	10 (9.26)	
Former	1,397 (45.80)	838 (59.31)	46 (70.77)		473 (32.31)	40 (37.04)	
Never	1,337 (43.84)	422 (29.87)	13 (20.00)		844 (57.65)	58 (53.70)	
Alcohol use, n (%)				0.2			0.8
Current	1,505 (49.49)	813 (57.78)	30 (46.88)		615 (42.07)	47 (43.52)	
Former	677 (22.26)	362 (25.73)	20 (31.25)		277 (18.95)	18 (16.67)	
Never	859 (28.25)	232 (16.49)	14 (21.88)		570 (38.99)	43 (39.81)	
Healthcare							
Primary care provider, n (%)	2,878 (94.48)	1,323 (93.63)	65 (100.00)	0.03	1,384 (94.73)	106 (99.07)	0.06
Supplemental health insurance for medications, n (%)	1,883 (63.02)	868 (62.63)	40 (61.54)	0.9	905 (63.24)	70 (66.04)	0.6
Influenza vaccine in the past year, n (%)	2,103 (69.13)	996 (70.69)	48 (73.85)	0.6	983 (67.33)	76 (70.37)	0.5

Table 3.2 Baseline characteristics of users and non-users of antidepressant medications by gender

Characteristics	Total N = 3,055	Men N = 1,481			Women N = 1,574		
		Non-users N = 1,424	Users N = 57	p-value	Non-users N = 1,461	Users N = 113	p-value
Demographics							
Age (years), mean ± SD	73.63 ± 2.87	73.77 ± 2.88	73.77 ± 2.56	0.9	73.52 ± 2.87	73.22 ± 2.84	0.3
Race (African-American), n (%)	1,266 (41.44)	526 (36.94)	17 (29.82)	0.3	690 (47.23)	33 (29.20)	<0.001
Education (less than high school), n (%)	766 (25.14)	387 (27.22)	15 (26.32)	0.9	347 (23.83)	17 (15.18)	0.04
Marital status (married), n (%)	1,568 (54.81)	979 (72.52)	46 (83.64)	0.07	498 (36.83)	45 (43.27)	0.2
Family income ($25,000 or less), n (%)	1,402 (52.24)	554 (43.18)	22 (39.29)	0.6	768 (61.64)	58 (58.59)	0.5
Clinic site (Pittsburgh), n (%)	1,516 (49.62)	715 (50.21)	21 (36.84)	0.05	721 (49.35)	59 (52.21)	0.6
Health status							
Self-rated health (poor/fair), n (%)	493 (16.16)	227 (15.95)	16 (28.07)	0.02	229 (15.71)	21 (18.58)	0.4
Co-morbid medical conditions (3 or more), n (%)	520 (18.20)	246 (18.58)	15 (29.41)	0.05	236 (17.14)	23 (21.90)	0.2
Limitation due to hearing problems, n (%)	269 (8.88)	175 (12.40)	6 (10.53)	0.7	77 (5.31)	11 (9.91)	0.04
Limitation due to vision problems, n (%)	268 (8.79)	131 (9.23)	8 (14.04)	0.2	119 (8.15)	10 (8.85)	0.8
IADL limitations (any), n (%)	372 (14.63)	96 (8.41)	8 (18.18)	0.02	239 (18.91)	29 (31.18)	<0.01
BMI, mean ± SD	27.40 ± 4.82	27.08 ± 3.91	26.73 ± 5.11	0.5	27.75 ± 5.54	27.25 ± 4.86	0.4
Any bodily pain, n (%)	1,999 (65.50)	852 (59.92)	36 (63.16)	0.6	1,025 (70.21)	86 (76.11)	0.2
Poor sleep, n (%)	344 (11.33)	143 (10.08)	6 (10.53)	0.9	172 (11.88)	23 (20.72)	0.01
Anxiety, n (%)	430 (14.18)	152 (10.73)	12 (21.43)	0.01	232 (16.02)	34 (30.63)	<0.001
Depression, n (%)	144 (4.75)	52 (3.67)	4 (7.27)	0.2	70 (4.83)	18 (16.22)	<0.001
3MS (score), mean ± SD	90.07 ± 8.40	89.52 ± 8.70	89.25 ± 7.56	0.5	90.56 ± 8.18	90.94 ± 7.26	0.9
Life style							
Smoking status, n (%)				0.1			0.6
Current	316 (10.36)	149 (10.49)	10 (17.54)		143 (9.80)	14 (12.39)	
Former	1,397 (45.80)	849 (59.75)	35 (61.40)		480 (32.90)	33 (29.20)	
Never	1,337 (43.84)	423 (29.77)	12 (21.05)		836 (57.30)	66 (58.41)	
Alcohol use, n (%)				0.2			0.8
Current	1,505 (49.49)	817 (57.74)	26 (46.43)		611 (41.94)	51 (45.13)	

Table 3.2 Continued

Former	677 (22.26)	363 (25.65)	19 (33.93)		274 (18.81)	21 (18.58)	
Never	859 (28.25)	235 (16.61)	11 (19.64)		572 (39.26)	41 (36.28)	
Healthcare							
Primary care provider, n (%)	2,878 (94.48)	1,331 (93.67)	57 (100.00)	0.05	1,381 (94.91)	109 (96.46)	0.7
Supplemental health insurance for medications, n (%)	1,883 (63.02)	873 (62.63)	35 (61.40)	0.9	901 (63.23)	74 (66.07)	0.5
Influenza vaccine in the past year, n (%)	2,103 (69.13)	995 (70.22)	49 (85.96)	0.01	981 (67.33)	78 (70.27)	0.5

Table 3.3 Proportion of anxiolytic and antidepressant medications users by gender for each visit

Medication class	Baseline N = 3,055	Year 6 N = 2,515	Year 11 N = 1,337	p for trend
BZDs, n (%)				
Men	51 (1.67)	49 (1.95)	36 (2.69)	0.01
Women	83 (2.72)	71 (2.82)	54 (4.04)	0.04
NBZDs, n (%)				
Men	15 (0.49)	5 (0.20)	12 (0.90)	0.09
Women	28 (0.92)	15 (0.60)	16 (1.20)	0.4
SNRIs, n (%)				
Men	2 (0.07)	5 (0.20)	6 (0.45)	0.02
Women	1 (0.03)	4 (0.16)	11 (0.82)	<0.01
SSRIs, n (%)				
Men	28 (0.92)	68 (2.70)	45 (3.37)	<0.001
Women	57 (1.87)	106 (4.21)	59 (4.41)	<0.001
TCAs, n (%)				
Men	29 (0.95)	16 (0.64)	4 (0.30)	0.04
Women	57 (1.87)	35 (1.39)	22 (1.65)	0.5
Total*				
Men	110 (3.60)	128 (5.09)	85 (6.36)	<0.001
Women	202 (6.61)	204 (8.11)	141 (10.55)	<0.001

*Total is less than sum of individual classes as some participants were taking multiple medications.

Table 3.4 Predictors of anxiolytic and antidepressant medications in the full sample

	Anxiolytic medications		Antidepressant medications	
	Univariable	Multivariable*	Univariable	Multivariable*
	Odds Ratio (95% Confidence Interval)			
Gender				
Female	1.44 (1.12, 1.86)		1.55 (1.24, 1.94)	1.63 (1.20, 2.22)
Male	1.00 (reference)		1.00 (reference)	1.00 (reference)
Age (years)	0.98 (0.94, 1.02)		0.99 (0.95, 1.03)	
Race				
African-American	0.62 (0.47, 0.80)	0.59 (0.41, 0.86)	0.51 (0.40, 0.64)	0.48 (0.35, 0.65)
Caucasian	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Education				
Less than high school	1.07 (0.80, 1.42)		0.78 (0.59, 1.02)	
High school or more	1.00 (reference)		1.00 (reference)	
Marital status				
Married	0.99 (0.77, 1.26)		0.92 (0.74, 1.14)	
Not married	1.00 (reference)		1.00 (reference)	
Family income				
$25,000 or less	1.18 (0.91, 1.53)	1.48 (1.03, 2.12)	0.90 (0.72, 1.14)	
More than $25,000	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Self-rated health				
Poor/fair	1.71 (1.34, 2.19)		1.28 (1.02, 1.61)	
Good/excellent	1.00 (reference)		1.00 (reference)	
Co-morbid medical conditions				
3 or more	1.69 (1.25, 2.29)	1.78 (1.22, 2.61)	1.34 (1.02, 1.77)	
0-2	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Limitation due to hearing problems				
Yes	1.23 (0.81, 1.85)		1.31 (0.93, 1.86)	
No	1.00 (reference)		1.00 (reference)	
Limitation due to vision problems				
Yes	0.74 (0.45, 1.22)		1.22 (0.85, 1.75)	
No	1.00 (reference)		1.00 (reference)	
IADL limitations				
Any	1.76 (1.27, 2.45)	1.69 (1.12, 2.55)	2.24 (1.69, 2.98)	1.86 (1.31, 2.65)
None	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
BMI	0.98 (0.96, 1.01)		1.00 (0.98, 1.02)	
Any bodily pain				
Yes	1.64 (1.23, 2.19)		1.46 (1.14, 1.86)	
No	1.00 (reference)		1.00 (reference)	
Poor sleep				
Yes	1.30 (0.91, 1.86)		1.53 (1.13, 2.08)	
No	1.00 (reference)		1.00 (reference)	
Anxiety				
Yes	2.43 (1.82, 3.23)	2.31 (1.64, 3.26)	2.18 (1.69, 2.82)	1.54 (1.13, 2.10)
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Depression				

Table 3.4 Continued

Yes	1.91 (1.43, 2.57)		2.29 (1.76, 2.96)	2.25 (1.55, 3.25)
No	1.00 (reference)		1.00 (reference)	1.00 (reference)
3MS (score)	0.98 (0.97, 1.00)		1.00 (0.99, 1.02)	
Smoking status				
Current	1.24 (0.78, 1.98)		1.23 (0.78, 1.94)	
Former	1.17 (0.89, 1.54)		0.89 (0.68, 1.15)	
Never	1.00 (reference)		1.00 (reference)	
Alcohol use				
Current	0.72 (0.53, 0.99)		0.95 (0.71, 1.28)	
Former	0.97 (0.70, 1.34)		0.83 (0.60, 1.17)	
Never	1.00 (reference)		1.00 (reference)	
Primary care provider				
Yes	2.42 (1.18, 5.00)	3.43 (1.21, 9.72)	3.18 (1.44, 7.02)	
No	1.00 (reference)		1.00 (reference)	
Supplemental health insurance for medications				
Yes	0.93 (0.72, 1.19)		1.05 (0.84, 1.32)	
No	1.00 (reference)		1.00 (reference)	
Influenza vaccine in the past year				
Yes	1.26 (0.95, 1.68)		1.55 (1.19, 2.02)	
No	1.00 (reference)		1.00 (reference)	

*Adjusted for clinic site.

Table 3.5 Predictors of anxiolytic medications use by gender

	Men		Women	
	Univariable	Multivariable*	Univariable	Multivariable*
	Odds Ratio (95% Confidence Interval)			
Age (years)	1.03 (0.96, 1.10)		0.95 (0.90, 1.01)	
Race				
African-American	0.53 (0.33, 0.83)	0.50 (0.29, 0.85)	0.63 (0.45, 0.87)	0.60 (0.39, 0.91)
Caucasian	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Education				
Less than high school	0.98 (0.63, 1.53)		1.17 (0.81, 1.70)	
High school or more	1.00 (reference)		1.00 (reference)	
Marital status				
Married	1.85 (1.20, 2.85)		0.86 (0.61, 1.22)	
Not married	1.00 (reference)		1.00 (reference)	
Family income				
$25,000 or less	0.91 (0.60, 1.39)		1.28 (0.90, 1.81)	1.84 (1.19, 2.85)
More than $25,000	1.00 (reference)		1.00 (reference)	1.00 (reference)
Self-rated health				
Poor/fair	1.60 (1.09, 2.34)	2.06 (1.26, 3.37)	1.72 (1.25, 2.36)	
Good/excellent	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Co-morbid medical conditions				
3 or more	2.10 (1.32, 3.35)	1.92 (1.14, 3.21)	1.49 (1.00, 2.23)	
0-2	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Limitation due to hearing problems				
Yes	1.32 (0.75, 2.30)		1.35 (0.73, 2.50)	
No	1.00 (reference)		1.00 (reference)	
Limitation due to vision problems				
Yes	0.42 (0.17, 1.02)		1.01 (0.55, 1.84)	
No	1.00 (reference)		1.00 (reference)	
IADL limitations				
Any	2.19 (1.17, 4.12)		1.50 (1.02, 2.20)	
None	1.00 (reference)		1.00 (reference)	
BMI	0.98 (0.94, 1.02)		0.98 (0.95, 1.01)	
Any bodily pain				
Yes	1.50 (0.97, 2.31)		1.63 (1.10, 2.41)	
No	1.00 (reference)		1.00 (reference)	
Poor sleep				
Yes	0.93 (0.47, 1.86)		1.48 (0.97, 2.24)	
No	1.00 (reference)		1.00 (reference)	
Anxiety				
Yes	2.20 (1.34, 3.61)	1.93 (1.15, 3.24)	2.51 (1.75, 3.59)	2.40 (1.66, 3.48)
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Depression				
Yes	1.64 (0.94, 2.85)		2.02 (1.44, 2.85)	
No	1.00 (reference)		1.00 (reference)	
3MS (score)	0.99 (0.97, 1.01)		0.98 (0.97, 1.00)	
Smoking status				
Current	1.81 (0.81, 4.07)		1.25 (0.68, 2.27)	

Table 3.5 Continued

Former	2.00 (1.18, 3.42)		1.11 (0.78, 1.57)	
Never	1.00 (reference)		1.00 (reference)	
Alcohol use				
Current	0.90 (0.48, 1.69)		0.79 (0.54, 1.15)	
Former	1.33 (0.72, 2.49)		0.95 (0.63, 1.43)	
Never	1.00 (reference)		1.00 (reference)	
Primary care provider				
Yes	3.71 (0.88, 15.60)		1.90 (0.82, 4.39)	
No	1.00 (reference)		1.00 (reference)	
Supplemental health insurance for medications				
Yes	1.04 (0.69, 1.58)		0.86 (0.62, 1.18)	
No	1.00 (reference)		1.00 (reference)	
Influenza vaccine in the past year				
Yes	1.20 (0.75, 1.94)		1.34 (0.94, 1.91)	
No	1.00 (reference)		1.00 (reference)	

*Adjusted for clinic site.

Table 3.6 Predictors of antidepressant medications use by gender

	Men		Women	
	Univariable	Multivariable*	Univariable	Multivariable*
	Odds Ratio (95% Confidence Interval)			
Age (years)	1.01 (0.96, 1.07)		0.98 (0.93, 1.03)	
Race				
African-American	0.51 (0.34, 0.77)	0.42 (0.24, 0.73)	0.46 (0.34, 0.62)	0.50 (0.34, 0.72)
Caucasian	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Education				
Less than high school	0.87 (0.57, 1.33)		0.74 (0.52, 1.06)	
High school or more	1.00 (reference)		1.00 (reference)	
Marital status				
Married	0.97 (0.68, 1.40)		1.12 (0.84, 1.51)	
Not married	1.00 (reference)		1.00 (reference)	
Family income				
$25,000 or less	0.68 (0.46, 0.99)		0.96 (0.71, 1.31)	
More than $25,000	1.00 (reference)		1.00 (reference)	
Self-rated health				
Poor/fair	1.51 (1.05, 2.15)	1.61 (1.04, 2.51)	1.17 (0.88, 1.57)	
Good/excellent	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Co-morbid medical conditions				
3 or more	1.44 (0.93, 2.23)		1.32 (0.92, 1.89)	
0-2	1.00 (reference)		1.00 (reference)	
Limitation due to hearing problems				
Yes	1.09 (0.65, 1.84)		2.03 (1.26, 3.27)	
No	1.00 (reference)		1.00 (reference)	
Limitation due to vision problems				
Yes	1.27 (0.71, 2.28)		1.21 (0.76, 1.92)	
No	1.00 (reference)		1.00 (reference)	
IADL limitations				
Any	1.90 (0.99, 3.62)	2.06 (1.01, 4.21)	2.15 (1.55, 2.99)	1.81 (1.22, 2.68)
None	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
BMI	1.03 (0.98, 1.08)		0.98 (0.96, 1.01)	
Any bodily pain				
Yes	1.21 (0.84, 1.73)		1.56 (1.11, 2.19)	
No	1.00 (reference)		1.00 (reference)	
Poor sleep				
Yes	1.25 (0.74, 2.10)		1.64 (1.13, 2.40)	
No	1.00 (reference)		1.00 (reference)	
Anxiety				
Yes	2.51 (1.59, 3.97)		1.92 (1.42, 2.60)	1.48 (1.03, 2.14)
No	1.00 (reference)		1.00 (reference)	1.00 (reference)
Depression				
Yes	1.77 (1.11, 2.83)		2.45 (1.80, 3.35)	2.67 (1.72, 4.16)
No	1.00 (reference)		1.00 (reference)	1.00 (reference)
3MS (score)	1.00 (0.98, 1.02)		1.00 (0.99, 1.02)	
Smoking status				
Current	2.15 (0.98, 4.69)		1.20 (0.68, 2.09)	

Table 3.6 Continued

Former	1.62 (0.99, 2.66)		0.82 (0.58, 1.16)	
Never	1.00 (reference)		1.00 (reference)	
Alcohol use				
Current	1.17 (0.63, 2.19)		1.11 (0.78, 1.57)	
Former	1.20 (0.62, 2.31)		0.86 (0.57, 1.31)	
Never	1.00 (reference)		1.00 (reference)	
Primary care provider				
Yes	8.41 (1.18, 60.18)		2.19 (0.91, 5.25)	
No	1.00 (reference)		1.00 (reference)	
Supplemental health insurance for medications				
Yes	0.94 (0.65, 1.34)		1.13 (0.85, 1.52)	
No	1.00 (reference)		1.00 (reference)	
Influenza vaccine in the past year				
Yes	1.97 (1.26, 3.07)	1.97 (1.09, 3.56)	1.42 (1.02, 1.98)	
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	

*Adjusted for clinic site.

4.0 PAPER 2: ANXIETY SYMPTOMS AND RISK OF DEMENTIA AND MILD COGNITIVE IMPAIRMENT IN THE OLDEST OLD WOMEN

4.1 ABSTRACT

Background: Research investigating anxiety as a predictor of future cognitive decline in older adults is limited and findings conflict. We examined the relationship between level and changes of anxiety symptoms, and subsequent dementia and mild cognitive impairment (MCI) in the oldest old women. **Methods:** We studied 1,425 community-dwelling oldest old women (mean age = 82.8, SD ±3.1 years) who were followed on average for 4.9 years. The Goldberg Anxiety Scale was used to assess anxiety symptoms at baseline, and an expert clinical panel adjudicated dementia and MCI at follow-up. Participants with probable cognitive impairment (Mini-Mental State Examination score < 24, self-reported dementia diagnosis and use of medication) at baseline were excluded. **Results:** At baseline, there were 190 (13%) women who had moderate/severe anxiety symptoms and 403 (28%) who had mild anxiety symptoms. Women with mild or moderate/severe anxiety symptoms were more likely to also have depressed mood, poor sleep, more chronic medical conditions and more impairments in daily living activities compared to those with no anxiety symptoms. Compared to those with no anxiety symptoms at baseline, women with mild anxiety symptoms were more likely to develop dementia at follow-up (adjusted odds ratio = 1.66, 95% confidence interval 1.12, 2.45). No significant association was

observed between anxiety symptoms and MCI. **Conclusion:** In the oldest old women, our findings suggest that mild and unstable anxiety symptoms may predict future risk of dementia, but not MCI. Future studies should explore potential underlying biological mechanisms linking these unique characteristics of anxiety to cognitive impairment.

4.2 INTRODUCTION

In the United States, a nationally representative survey, the National Comorbidity Survey Replication, estimated the lifetime prevalence of any anxiety disorder as 16.6% and 9.6% among women and men aged 65 years and older, respectively.(Gum et al., 2009) Another nationally representative study, the Aging, Demographics and Memory Study, reported the prevalence of dementia as 16% and 11% among women and men aged 70 years and older, respectively.(Plassman et al., 2007) Both conditions have been related to several adverse health outcomes including increased disability and mortality.(WHO, 2012; Wolitzky-Taylor et al., 2010)

Multiple lines of evidence support a significant association between both conditions. First, cross-sectional studies documented lower cognitive function in older adults with heightened anxiety (Beaudreau & O'Hara, 2009; Bierman et al., 2005; Mantella et al., 2007; Wetherell et al., 2002), and elevated anxiety symptoms in older adults with cognitive impairment.(Andreescu et al., 2014; Geda et al., 2008; Lopez et al., 2003; Lyketsos et al., 2002) Second, longitudinal studies suggested that anxiety increased the risk of progression of mild cognitive impairment (MCI) to dementia.(Gallagher et al., 2011; Palmer et al., 2007) Third, a number of studies reported that the use of benzodiazepines, a class of anxiolytic medications, was associated with risk of cognitive impairment or decline.(Billioti de Gage et al., 2012; Gallacher et al., 2012; Lagnaoui et al., 2002; Paterniti et al., 2002) This may indicate that benzodiazepine use is a marker of an underlying condition, such as anxiety, that led to the reported association.(Yaffe & Boustani, 2014) Finally, there is a high co-occurrence between

anxiety and depression(Byers et al., 2010; Kessler et al., 2003), which itself is a potential risk factor for cognitive impairment.(Byers & Yaffe, 2011; Ganguli, 2009)

The longitudinal relationship between anxiety and subsequent cognitive impairment in older adults remains unclear.(Beaudreau & O'Hara, 2008) Previous research examining this relationship was inconclusive, and was limited by small sample size, short follow-up, not accounting for important confounders and measurement issues.(Bierman et al., 2008; Burton et al., 2013; Cherbuin et al., 2009; de Bruijn et al., 2014; Gallacher et al., 2009); Okereke and Grodstein (2013); (Pietrzak et al., 2012; Potvin, Forget, et al., 2011; Sinoff & Werner, 2003) Finally, previous studies did not investigate how specific characteristics of anxiety are related to each level of cognitive impairment. Therefore, additional research is needed to understand the role of anxiety as a predictor of future cognitive impairment and whether anxiety can early identify those at higher risk or is a potentially modifiable risk factor.

Anxiety disorders are more prevalent in women than men and have been associated with more disability in women than men.(Byers et al., 2010) (Baxter et al., 2014) Therefore, it is important to examine the relationship between anxiety and cognitive impairment separately for men and women. We are not aware of any prospective study that focused on the oldest old women (age 80 and above), the fastest growing segment of the population in the United States. (U.S.CensusBureau, 2014)

In this longitudinal study, we examined the association between presence, level and changes of anxiety symptoms and risk of subsequent dementia, MCI and decline in cognitive functioning among oldest old women enrolled in the Study of Osteoporotic Fractures. We hypothesized that severe and persistent anxiety symptoms will be associated with increased risk of dementia, MCI and poor cognitive function.

4.3 METHODS

4.3.1 Population

We utilized data from the Study of Osteoporotic Fractures (SOF)(Cummings et al., 1995), a prospective cohort study of community-dwelling women aged 65 years and older in 1986-1988 (SOF visit 1). In brief, 9,704 predominantly Caucasian older women were recruited from population-based listings in 4 locations in the United States as follows: Baltimore, Maryland; Minneapolis, Minnesota; Monongahela Valley (near Pittsburgh), Pennsylvania; and Portland, Oregon. An additional 662 African-American older women were recruited during SOF visit 6 (1997-1998). Women were not enrolled in SOF if they were unable to walk without assistance or had undergone a bilateral hip replacement. The institutional review board at each site approved the study and participants provided written informed consent.

At SOF visit 9, 1,513 women from 3 of the 4 original SOF sites attended a clinic visit for a cognitive status assessment, and therefore participants from only those 3 sites were part of our study. For this study, we included 1,470 women (40% of survivors in participating sites) who had anxiety assessment at SOF visit 8 (2002-2004; baseline) and had cognitive status assessment at SOF visit 9 (2006-2008; follow-up). Of those 1,470 women with complete exposure and outcome data, we excluded 17 women with indeterminate cognitive status at follow-up. We additionally excluded 28 women with probable cognitive impairment at baseline, with the following overlapping criteria: self-report of dementia diagnosis (n = 4); self-report of dementia treatment (n = 5); and a Mini-Mental State Examination (MMSE)(Folstein, Folstein, & McHugh, 1975) score < 24 (n = 19). In total, 1,425 women constituted the analytical sample for our study.

4.3.2 Measurement of anxiety symptoms

At the baseline and follow-up visits, anxiety symptoms were measured using the Goldberg Anxiety Scale (GAS).(Goldberg et al., 1988) GAS is a 9-item self-report instrument that inquires about anxiety symptoms experienced in the past month. GAS items span various types of anxiety symptoms, and are rated as yes (1) or no (0) answers with a total score ranging from 0 to 9. Participants must answer yes to at least 2 of the first 4 items in order to have the subsequent 5 items included in their total score. The 4 screening items are as follows: being keyed up or on edge; worrying a lot; being irritable, and having difficulty relaxing. The recommended cutoff score of 5 suggests that a participant has a 50% chance of a clinically significant anxiety, while higher scores substantially increase the probability of a significant anxiety disturbance.

To study the level of anxiety symptoms, we classified participants according to baseline GAS score into the following 3 groups: no anxiety (0), mild anxiety (1-4), and moderate/severe anxiety (5-9). To study the change of anxiety symptoms over time, we classified participants according to baseline and follow-up GAS scores into the following 4 groups: never anxious (0 at baseline and follow-up), incident anxiety (0 at baseline and ≥ 5 at follow-up), persistent anxiety (≥ 5 at baseline and follow-up), and receded anxiety (≥ 5 at baseline and 0 at follow-up). To capture large changes over time, these 4 groups covered changes between both extremes of anxiety symptoms level (no symptoms versus moderate/severe symptoms), and as such they constituted only a subsample (N = 641) that did not include those with mild anxiety symptoms (Figure 4.6.1).

4.3.3 Measurement of clinical cognitive status

At the follow-up visit, a diagnosis of dementia or MCI was determined using a two-stage process. First, participants were screened for cognitive impairment according to one or more of the following 5 criteria: score < 88 on the Modified Mini-Mental State Examination (3MS)(Teng & Chui, 1987); score < 4 on the California Verbal Learning Test, Second Edition (CVLT-II) delayed recall(Delis, Kramer, Kaplan, & Ober, 2000); score ≥ 3.6 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)(Jorm & Jacomb, 1989); self-report of dementia diagnosis; or nursing home residence. Those who screened negative on all of the above were considered as having normal cognition, while a panel of clinical experts adjudicated those who screened positive on one or more of the above. The panel consisted of a geropsychologist, a neurologist and two neuropsychologists, who considered the following information for each participant: neuropsychological test scores; depression score; functional status; medications, and medical history. Diagnoses of dementia and MCI were made according to DSM-IV criteria (American Psychiatric Association, 2000) and modified Petersen criteria (Petersen et al., 2001), respectively. Further details about the above clinical adjudication process have been published elsewhere.(Yaffe et al., 2011)

4.3.4 Measurement of cognitive function

At the baseline and follow-up visits, a shorter version of the MMSE (in which questions regarding language were left out) was administered.(Yaffe et al., 2011) The short MMSE scores ranged from 0 to 26, with lower scores indicating poorer cognitive function. Clinically significant cognitive decline was defined as the change in short MMSE score of at least one

standard deviation from mean change from baseline to follow-up. This difference was equivalent to a loss of 3.33 or more MMSE points over time. The reference group included participants who declined less than one standard deviation, those who maintained their scores and those with improved scores.

At the follow-up visit, an expanded neuropsychological test battery was administered to participants. Tests included the 3MS, the Trails B(Reitan & Wolfson, 1985), the CVLT-II with immediate and 10-minute delay scores, Digit Span with forward and backward scores(Wechsler, 1997), and verbal fluency tests(Spreen & Strauss, 1991). Tests assessed multiple cognitive domains including global cognition (3MS), executive function and psychomotor speed (Trails B), verbal learning and memory (CVLT-II), attention (forward Digit Span), working memory (backwards Digit Span), phonemic fluency (naming as many words beginning with "f"), and category fluency (naming as many vegetables).

4.3.5 Other measurements

At the baseline visit, additional measurements were collected via self-report questionnaires. Demographic information included age, education, race and marital status. Medical history was defined as prior physician diagnosis of select medical conditions. Participants reported smoking status, alcohol use, caffeine intake, whether or not the participant walked for exercise, and self-rated health status. Functional status was assessed by collecting information on difficulty with 6 instrumental activities of daily living (IADL), which included walking 2 to 3 blocks on level ground, climbing up to 10 steps, walking down 10 steps, preparing meals, doing heavy housework, and shopping for groceries or clothing. The number of activities that were difficult was summed for a total IADL score. The Geriatric Depression Scale (GDS)(Lyness et al., 1997)

was used to assess depressive symptoms, with the standard cutoff score of 6 or more used to define depression. The Pittsburgh Sleep Quality Index (PSQI)(Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was used to assess sleep, with the standard cutoff score of 5 or more used to define poor sleep. Medication use was ascertained by asking participants to bring all current prescription and non-prescription medications used in the past month to their clinic visits, while an interviewer collected this information in home visits. Medications were coded and categorized using the Iowa Drug Information Service (IDIS) scheme.(Pahor et al., 1994)

4.3.6 Statistical analysis

We calculated descriptive statistics for all variables and compared participants by level of anxiety symptoms at baseline and by clinical cognitive status at follow-up. For these comparisons, we used chi-squared test (or Fisher's exact test for low expected cell counts) for categorical variables, one-way ANOVA for normally distributed continuous data and the Kruskal Wallis test for skewed continuous data. Next, a series of unadjusted and multivariable-adjusted logistic regression models of the relationship between anxiety symptoms, and dementia and MCI were fit. Similarly, linear regression models were fit for cognitive function tests. Based on literature (Zeki Al Hazzouri et al., 2014), multivariable models were adjusted for the following potential confounders: demographics (age, education and marital status), health behaviors (smoking, alcohol use and exercise), medical history (hypertension, myocardial infarction, stroke, and diabetes), psychotropic medications (benzodiazepine, non-benzodiazepine non-barbiturate sedative hypnotic and antidepressant), depression and poor sleep. All statistical analyses were conducted with Stata version 13.1 (StataCorp LP, College Station, TX, USA).

4.4 RESULTS

4.4.1 Characteristics of participants

Baseline characteristics of participants are presented in Tables 4.6.1 and 4.6.2. At baseline (mean age = 82.8 years), there were 190 (13%) women who had moderate/severe anxiety symptoms and 403 (28%) who had mild anxiety symptoms. Women with moderate/severe or mild anxiety symptoms at baseline were more likely to be married, have depressed mood and poor sleep, take more psychotropic medications, suffer from more chronic medical conditions, and have more impairments in daily living activities compared to those with no anxiety symptoms. After mean follow-up time of 4.9 (standard deviation [SD] ±0.6) years, 233 (16%) women developed dementia and 335 (24%) women developed MCI. Women with dementia or MCI at follow-up were more likely to be older, have high school education or less, have depressed mood, take more antidepressants, exercise less and have more impairments in daily living activities compared to those who maintained normal cognition.

4.4.2 Anxiety symptoms and clinical cognitive status

The models of clinical cognitive status by anxiety symptoms are presented in Table 4.6.3. Women with mild anxiety symptoms at baseline were 1.58 times more likely to develop dementia at follow-up compared to those with no anxiety symptoms at baseline. This association remained statistically significant after controlling for potential confounding factors with a multivariable-adjusted odds ratio [OR] of 1.66 (95% confidence interval [CI] 1.12, 2.45). Moderate/severe anxiety symptoms, however, were not significantly associated with risk of

dementia (multivariable-adjusted OR = 1.27, 95% CI 0.71, 2.28). Overall, anxiety remained a significant predictor of dementia in the multivariable-model (Wald (2) = 6.34, p = 0.04). There were also no significant association between any level of anxiety symptoms and risk of MCI.

Women who had moderate/severe anxiety symptoms at baseline and did not have any anxiety symptoms at follow-up (receded anxiety) were 3.80 times more likely to develop dementia at follow-up compared to those who were never anxious. Similarly, women who did not have any anxiety symptoms at baseline and developed moderate/severe anxiety symptoms at follow-up (incident anxiety) were 1.85 times more likely to develop dementia at follow-up compared to those who were never anxious. However, this association did not remain significant after controlling for potential confounding factors (multivariable-adjusted OR = 1.54, 95% CI 0.74, 3.20). Persistent anxiety symptoms over time were not significantly associated with dementia. There were no significant association between any change of anxiety symptoms over time and risk of MCI.

Examining a curvilinear relationship between anxiety symptoms and cognitive impairment revealed a significant quadratic term for anxiety score and odds of developing dementia (Figure 4.6.2), but not MCI.

4.4.3 Anxiety symptoms and cognitive function tests

The models of cognitive function tests by anxiety symptoms are presented in Table 4.6.4. Compared to women with no anxiety symptoms at baseline, those with mild anxiety symptoms at baseline performed significantly worse on tests for verbal learning and memory (CVLT-II) and working memory (Backwards Digits Span). Those with moderate/severe anxiety symptoms performed significantly worse only on category fluency test.

Compared to women who were never anxious, those with receded anxiety symptoms performed significantly worse on 3MS (4.98 points reduction) and CVLT-II 10-minute delayed recall (1.33 points reduction). Those with incident anxiety symptoms performed significantly worse on only 3MS (3.04 points reduction).

4.4.4 Anxiety symptoms and clinically significant cognitive decline

In total, 256 (19%) women had clinically significant cognitive decline in short MMSE over time. Compared to women with no anxiety symptoms at baseline, women with mild anxiety symptoms were more likely to have cognitive decline (OR = 1.40, 95% CI 1.04, 1.90). However, this association did not remain significant after controlling for potential confounding factors (multivariable-adjusted OR = 1.24, 95% CI 0.87, 1.76). Moderate/severe anxiety symptoms or change in anxiety symptoms over time were not significantly associated with cognitive decline (data not shown).

4.5 DISCUSSION

This prospective study showed that mild anxiety symptoms in the oldest old women were associated with increased odds of incident dementia over a period of five years, independent of multiple confounders including depression. Change in anxiety symptoms over time, as denoted by incident and receded anxiety symptoms, was associated with dementia. Our study also showed that verbal and working memory were the principal cognitive domains affected by these characteristics of anxiety symptoms. To our knowledge, this is the first study to assess the relationship between characteristics of anxiety symptoms and subsequent development of dementia and MCI in the oldest old community-dwelling women.

This study is consistent with previous work that showed significant association between anxiety and subsequent cognitive impairment.(Burton et al., 2013; Gallacher et al., 2009; Geda et al., 2014; Pietrzak et al., 2012; Potvin, Forget, et al., 2011; Sinoff & Werner, 2003) For instance, Gallacher et al. (2009) reported that heightened anxiety was associated with clinically assessed cognitive impairment in 1,160 older men (aged 48 to 67 years) after 17 years of follow-up. Our work extends this finding to oldest old women. Few previous studies examined gender differences in the relationship between anxiety and subsequent cognitive impairment. Potvin et al. (2011) studied 1,942 older adults and reported that anxiety symptoms, but not disorders, were associated with cognitive impairment in women after one year of follow-up. In this same study, anxiety disorders, but not symptoms, were associated with cognitive impairment in men. Our findings are consistent with this finding in women. However, it is important to note that other studies did not find significant association between anxiety and subsequent cognitive

impairment.(Bierman et al., 2008; Cherbuin et al., 2009; de Bruijn et al., 2014) Finally, our study was in line with one previous study that found a significant quadratic relationship between level of anxiety and cognitive function(Bierman et al., 2008). However, our study found that mild anxiety symptoms were deleterious for cognitive status, whereas the other study found improvement in cognitive function with lower level of anxiety symptoms.

Three hypotheses have been advanced in the literature attempting to explain the relationship between anxiety and cognitive impairment. First, anxiety could be a risk factor for cognitive impairment. To support this etiological hypothesis, a dose-response relationship is to be expected where increasing level of anxiety symptoms will be associated with increasing level of cognitive impairment. Our findings showed that mild but not moderate/severe anxiety symptoms were associated with severe but not mild cognitive impairment and as such our study does not support this hypothesis. This is based on an assumption that both levels of anxiety symptoms and cognitive impairment reflect similar pathological processes across levels, which cannot be confirmed or ruled out by our measurements. Persistent anxiety symptoms over time were not associated with risk of cognitive impairment, yielding additional support to this conclusion. Second, the association between anxiety and cognitive impairment could be confounded by shared risk factors, such as depression. However, we controlled for a large number of potential confounders and therefore this hypothesis is unlikely to explain our findings.

Third, anxiety could be a consequence of cognitive impairment. Dementia is a degenerative disease with a long prodromal period and thus it is plausible that anxiety may appear as an early symptom or as a reaction to subtle cognitive deficits before formal diagnosis of a significant cognitive impairment. Thus, our follow-up duration of five years may have been too short to rule out this hypothesis. Our findings could be explained by this hypothesis if we

viewed mild anxiety symptoms as "prodromal symptoms" of undiagnosed cognitive impairment and moderate/severe anxiety symptoms as "true symptoms" of an anxiety disorder. This is further supported in our study by the finding that changes, but not persistence, in anxiety symptoms over time were associated with dementia. The unstable course in anxiety symptoms, denoted by the incident and receded groups, may indicate a gradual change in anxiety symptoms over time, which mirrors mild anxiety symptoms or prodromal symptoms. As we did not have additional measurements of anxiety between baseline and follow-up, this is a strong assumption to make. The association of incident and receded anxiety symptoms (representing two contrasting groups) with risk of dementia may reflect the clinical and pathological heterogeneity in our sample. While some individuals with cognitive impairment may have poor judgment and loss of perception, hindering their anxiety reporting, some may not. (AmericanPsychiatricAssociation, 2013) Clinical and pathological heterogeneity may also explain our finding of no significant association between anxiety and MCI.

Strengths of this study include the prospective cohort design, a large, well-characterized cohort of community-dwelling oldest old women, clinical adjudication of cognitive impairment by an expert panel and consideration of a large number of possible confounders. Our study has several limitations. First, our sample was comprised of mostly Caucasian oldest old women, which hinders generalizability of findings to younger women, other ethnic groups and men. Second, anxiety symptoms were self-reported and were measured by an instrument that was developed in young adults. However, GAS has shown moderate validity in a sample of older adults.(Pachana et al., 2007) Third, we did not exclude participants with probable cognitive impairment based on clinical measures and therefore our sample may have included participants with subtle cognitive impairment. We used established criteria to exclude those participants who

showed signs of cognitive impairment. Finally, we could not control for residual confounding inherent in the observational design of the study.

Our findings suggest that anxiety symptoms in cognitively healthy oldest old women may serve as an important predictor of future risk of dementia. This finding is independent of depression, poor sleep, use of psychotropic medications and other important confounders. Future studies should explore potential underlying biological mechanisms linking these unique characteristics of anxiety symptoms to cognitive impairment in older women.

4.6 TABLES AND FIGURES

Table 4.1 Baseline characteristics of participants according to level of anxiety symptoms at baseline

Characteristics	Total N = 1,425	Anxiety symptoms			p-value
		No symptoms N = 832	Mild (1-4 symptoms) N = 403	Moderate/severe (5-9 symptoms) N = 190	
Demographics					
Age, years, mean ± SD	82.8 ± 3.1	82.8 ± 3.0	82.9 ± 3.2	82.6 ± 3.0	0.57
High school or less, n (%)	863 (60.8)	504 (60.9)	238 (59.2)	121 (63.7)	0.58
African-American, n (%)	156 (11.0)	84 (10.1)	48 (11.9)	24 (12.6)	0.46
Married, n (%)	429 (30.1)	201 (24.2)	144 (35.7)	84 (44.2)	<0.001
Medical history					
Stroke, n (%)	144 (10.1)	72 (8.7)	40 (9.9)	32 (16.8)	0.003
Myocardial infarction, n (%)	148 (10.4)	78 (9.4)	46 (11.4)	24 (12.6)	0.30
Congestive heart failure, n (%)	94 (6.6)	47 (5.7)	27 (6.7)	20 (10.5)	0.05
Hypertension, n (%)	853 (59.9)	493 (59.3)	243 (60.3)	117 (61.6)	0.82
Chronic obstructive pulmonary disease, n (%)	172 (12.1)	85 (10.2)	53 (13.2)	34 (17.9)	0.01
Diabetes, n (%)	145 (10.2)	85 (10.2)	43 (10.7)	17 (9.0)	0.81
Osteoarthritis, n (%)	537 (37.7)	272 (32.7)	171 (42.4)	94 (49.5)	<0.001
Rheumatoid arthritis, n (%)	108 (7.6)	59 (7.1)	32 (7.9)	17 (9.0)	0.65
Breast cancer, n (%)	146 (10.3)	83 (10.0)	37 (9.2)	26 (13.8)	0.21
Life style					
Take walks for exercise, n (%)	584 (41.4)	347 (42.1)	163 (40.8)	74 (39.6)	0.78
Number of drinks/week during past 30 days, mean ± SD	1.1 ± 2.8	1.0 ± 2.4	1.3 ± 3.3	1.2 ± 3.0	0.28
Current caffeine intake (mg/day), mean ± SD	157.3 ± 154.1	153.5 ± 154.7	167.2 ± 156.5	153.2 ± 145.6	0.30
Currently smoke cigarettes, n (%)	20 (1.6)	10 (1.3)	8 (2.3)	2 (1.2)	0.47
Quality of life					
Self-rated health status, good/excellent, n (%)	1,137 (79.8)	703 (84.5)	316 (78.4)	118 (62.1)	<0.001
Any IADL impairment, n (%)	650 (47.8)	332 (41.5)	200 (52.4)	118 (66.3)	<0.001
Pittsburgh Sleep Quality Index > 5, n (%)	765 (53.7)	364 (43.8)	230 (57.1)	171 (90.0)	<0.001
Geriatric Depression Scale ≥ 6, n (%)	121 (8.5)	22 (2.6)	42 (10.4)	57 (30.0)	<0.001
Psychotropic medications					
Benzodiazepine use in the past 30 days, n (%)	95 (7.0)	40 (5.0)	34 (8.9)	21 (11.7)	0.001
Non-benzodiazepine non-barbiturate sedative hypnotic use in the past 30 days, n (%)	13 (1.1)	4 (0.6)	4 (1.2)	5 (3.2)	0.018
Any antidepressant use in the past 30 days, n (%)	149 (10.9)	69 (8.6)	49 (12.8)	31 (17.2)	0.001

Table 4.1 Continued

SSRI antidepressant use in the past 30 days, n (%)	91 (6.7)	44 (5.5)	31 (8.1)	16 (8.9)	0.11
TCA antidepressant use in the past 30 days, n (%)	40 (2.9)	19 (2.4)	12 (3.1)	9 (5.0)	0.16

Table 4.2 Baseline characteristics of participants according to clinical cognitive status at follow-up

Characteristics	Total N = 1,425	Cognitive status			p-value
		Normal cognition N = 857	Mild cognitive impairment N = 335	Dementia N = 233	
Anxiety symptoms					0.09
Mild	403 (28.3)	227 (26.5)	94 (28.1)	82 (35.2)	
Moderate/severe	190 (13.3)	114 (13.3)	43 (12.8)	33 (14.2)	
Demographics					
Age, years, mean ± SD	82.8 ± 3.1	82.5 ± 2.8	82.9 ± 3.3	83.9 ± 3.5	0.001
High school or less, n (%)	863 (60.8)	480 (56.2)	234 (70.1)	149 (64.2)	<0.001
African-American, n (%)	156 (11.0)	83 (9.7)	45 (13.4)	28 (12.0)	0.15
Married, n (%)	429 (30.1)	269 (31.4)	91 (27.2)	69 (29.6)	0.35
Medical history					
Stroke, n (%)	144 (10.1)	76 (8.9)	36 (10.8)	32 (13.7)	0.08
Myocardial infarction, n (%)	148 (10.4)	78 (9.1)	40 (11.9)	30 (12.9)	0.14
Congestive heart failure, n (%)	94 (6.6)	58 (6.8)	20 (6.0)	16 (6.9)	0.87
Hypertension, n (%)	853 (59.9)	516 (60.2)	189 (56.4)	148 (63.5)	0.22
Chronic obstructive pulmonary disease, n (%)	172 (12.1)	105 (12.3)	42 (12.5)	25 (10.7)	0.78
Diabetes, n (%)	145 (10.2)	77 (9.0)	37 (11.0)	31 (13.3)	0.13
Osteoarthritis, n (%)	537 (37.7)	310 (36.2)	131 (39.1)	96 (41.2)	0.31
Rheumatoid arthritis, n (%)	108 (7.6)	61 (7.1)	29 (8.7)		0.66
Breast cancer, n (%)	146 (10.3)	87 (10.2)	31 (9.3)	28 (12.0)	0.56
Life style					
Take walks for exercise, n (%)	584 (41.4)	368 (43.4)	140 (42.0)	76 (33.2)	0.02
Number of drinks/week during past 30 days, mean ± SD	1.1 ± 2.8	1.2 ± 3.0	1.1 ± 2.8	0.6 ± 1.7	0.001
Current caffeine intake (mg/day), mean ± SD	157.3 ± 154.1	160.8 ± 156.5	158.8 ± 153.5	142.5 ± 145.5	0.28
Currently smoke cigarettes, n (%)	20 (1.6)	11 (1.4)	7 (2.4)	2 (1.0)	0.43
Quality of life					
Self-rated health status, good/excellent, n (%)	1,137 (79.8)	697 (81.3)	261 (77.9)	179 (76.8)	0.20
Any IADL impairment, n (%)	650 (47.8)	362 (44.0)	152 (47.7)	136 (62.4)	<0.001
Pittsburgh Sleep Quality Index > 5, n (%)	765 (53.7)	472 (55.1)	169 (50.5)	124 (53.2)	0.35
Geriatric Depression Scale ≥ 6, n (%)	121 (8.5)	53 (6.2)	35 (10.5)	33 (14.2)	<0.001
Psychotropic medications					
Benzodiazepine use in the past 30 days, n (%)	95 (7.0)	55 (6.7)	20 (6.2)	20 (9.2)	0.36
Non-benzodiazepine non-barbiturate sedative hypnotic use in the past 30 days, n (%)	13 (1.1)	8 (1.1)	1 (0.4)	4 (2.1)	0.22
Antidepressant use in the past 30 days, n (%)	149 (10.9)	65 (7.9)	41 (12.8)	43 (19.7)	<0.001

Table 4.3 Association between anxiety symptoms and dementia and mild cognitive impairment

	Anxiety symptoms	Dementia**		Mild cognitive impairment**	
		Unadjusted	Multivariable-adjusted*	Unadjusted	Multivariable-adjusted*
		Odds ratio (95% confidence interval)			
Model 1	Any	1.47 (1.10, 1.97)	1.56 (1.07, 2.26)	1.05 (0.81, 1.35)	1.07 (0.78, 1.47)
	None	1.00 (reference)			
Model 2	Moderate/severe	1.27 (0.82, 1.96)	1.27 (0.71, 2.28)	0.98 (0.67, 1.45)	0.99 (0.60, 1.62)
	Mild	1.58 (1.14, 2.18)	1.66 (1.12, 2.45)	1.08 (0.81, 1.44)	1.10 (0.79, 1.55)
	None	1.00 (reference)			
Model 3	Incident	1.85 (1.01, 3.39)	1.54 (0.74, 3.20)	2.26 (1.37, 3.73)	1.73 (0.95, 3.15)
	Persistent	1.08 (0.58, 2.03)	0.83 (0.34, 2.03)	0.96 (0.55, 1.67)	0.80 (0.38, 1.70)
	Receded	2.81 (1.17, 6.74)	3.80 (1.22, 11.87)	1.03 (0.37, 2.93)	1.10 (0.31, 3.84)
	Never	1.00 (reference)			

*Models are adjusted for demographics (age, education and marital status), health behaviors (smoking, alcohol use and exercise), medical history (hypertension, myocardial infarction, stroke, and diabetes), psychotropic medications (benzodiazepine, non-benzodiazepine non-barbiturate sedative hypnotic and antidepressant), depression and poor sleep.

**Reference group: normal cognition.

Table 4.4 Association between anxiety symptoms and cognitive function tests

Anxiety	3MS		Seconds to complete trails B		CVLT-II, immediate recall		CVLT-II, delayed recall		Forward Digit Span		Backward Digit Span		Verbal fluency test		Category fluency test	
	Regression coefficient p-value															
	Unadj.	Adj.*	Unadj.	Adj.*	Unadj.	Adj.*	Unadj.	Adj.*	Unadj.	Adj.*	Unadj.	Adj.*	Unadj.	Adj.*	Unadj.	Adj.*
Any anxiety symptom	-1.19 0.03	-1.15 0.06	3.95 0.09	2.86 0.28	-0.88 <0.01	-1.05 <0.01	-0.35 0.02	-0.40 0.02	-0.01 0.96	0.08 0.55	-0.22 0.05	-0.23 0.08	-0.14 0.52	-0.19 0.45	-0.37 0.06	-0.34 0.12
Level																
Mild anxiety	-1.23 0.05	-1.11 0.09	1.94 0.47	1.75 0.54	-0.86 0.01	-1.07 <0.01	-0.36 0.03	-0.43 0.02	-0.02 0.91	0.04 0.79	-0.27 0.03	-0.32 0.02	-0.11 0.67	-0.20 0.48	-0.19 0.38	-0.21 0.38
Moderate/severe anxiety	-1.10 0.18	-1.26 0.19	8.22 0.02	6.16 0.14	-0.93 0.04	-1.00 0.06	-0.34 0.12	-0.31 0.24	0.01 0.94	0.20 0.34	-0.12 0.48	0.04 0.86	-0.22 0.52	-0.18 0.65	-0.75 0.01	-0.73 0.03
Change																
Incident anxiety	-3.12 0.01	-3.04 0.02	4.68 0.34	-1.83 0.75	0.04 0.95	0.40 0.57	-0.08 0.79	0.03 0.93	-0.30 0.22	-0.25 0.37	-0.12 0.61	-0.07 0.80	-0.67 0.16	-0.20 0.71	-0.58 0.16	-0.57 0.21
Persistent anxiety	-0.23 0.84	0.68 0.63	9.21 0.06	4.59 0.44	-0.55 0.38	0.01 0.99	-0.19 0.54	0.05 0.91	-0.11 0.65	0.19 0.54	-0.30 0.21	-0.02 0.95	-0.55 0.25	0.18 0.76	-0.86 0.03	-0.70 0.16
Receded anxiety	-3.60 0.06	-4.98 0.03	13.47 0.09	14.20 0.12	-1.36 0.19	-2.00 0.10	-1.08 0.03	-1.33 0.03	0.20 0.64	0.05 0.91	0.07 0.86	-0.08 0.86	-0.71 0.37	-1.22 0.19	-1.20 0.08	-1.11 0.16

*Models are adjusted for demographics (age, education and marital status), health behaviors (smoking, alcohol use and exercise), medical history (hypertension, myocardial infarction, stroke, and diabetes), psychotropic medications (benzodiazepine, non-benzodiazepine non-barbiturate sedative hypnotic and antidepressant), depression and poor sleep.

Group	N (%)	Baseline	~5 years	Follow-up
Never anxious	410 (64)	No symptoms		No symptoms
Incident anxiety	102 (16)	No symptoms		Moderate/Severe symptoms
Persistent anxiety	100 (16)	Moderate/severe symptoms		Moderate/severe symptoms
Receded anxiety	29 (4)	Moderate/severe symptoms		No symptoms

Figure 4.1 Construction of four groups to study changes in anxiety symptoms over time

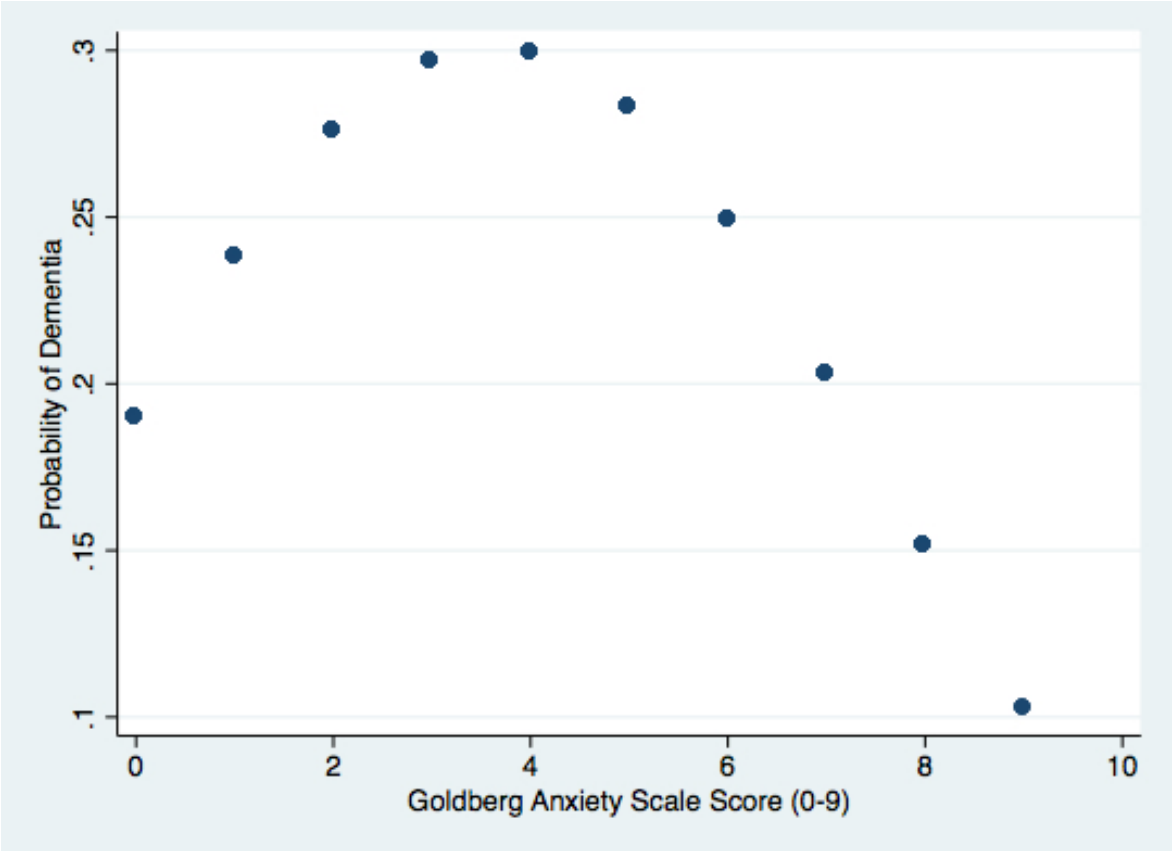


Figure 4.2 Probability of incident dementia by baseline anxiety score

5.0 PAPER 3: ANXIETY SYMPTOMS AND RISK OF COGNITIVE DECLINE IN OLDER MEN

5.1 ABSTRACT

Background: Previous research regarding anxiety as a predictor of future cognitive decline in older adults is limited and inconsistent. Depression, a commonly comorbid condition with anxiety, has been shown to be a potential risk factor for cognitive decline. We examined the independent relationship between anxiety symptoms and subsequent cognitive decline. **Methods:** We included 2,818 community-dwelling older men (mean age = 76.1, SD ±5.3 years) who were followed on average for 3.4 years. We assessed anxiety symptoms at baseline using the Goldberg Anxiety Scale (GAS; range = 0-9). We assessed cognitive function at baseline and at two subsequent visits using the Modified Mini-Mental State examination (3MS; global cognition) and the Trails B test (executive function). Clinically significant cognitive decline was defined as a reduction of 5 points or more in 3MS score or having worst decile of change in Trails B completion time. Participants with probable cognitive impairment (3MS score <80, use of dementia medication) at baseline were excluded. **Results:** At baseline, there were 690 (24%) men with mild anxiety symptoms (GAS 1-4) and 226 (8%) men with moderate/severe symptoms (GAS 5-9). Men with anxiety symptoms were more likely to have depressed mood, poor sleep, more chronic medical conditions and more impairment in activities of daily living compared to

those with no anxiety symptoms. Compared to those with no anxiety symptoms at baseline, men with any anxiety symptoms were more likely to have clinically significant worsening in Trails B completion time (OR = 1.56, 95% CI 1.19, 2.05). The association was attenuated after adjusting for potential confounders, including depression and poor sleep, but remained significant (OR = 1.40, 95% CI 1.04, 1.88). No significant association was observed between anxiety symptoms and clinically significant decline in 3MS. **Conclusion:** In older men, anxiety appears to be a potential independent predictor of clinically significant decline in executive function.

5.2 INTRODUCTION

Anxiety and cognitive impairment in older adults are major public health problems. In the United States, a nationally representative survey, the National Comorbidity Survey Replication, estimated the lifetime prevalence of any anxiety disorder as 16.6% and 9.6% among women and men aged 65 years and older, respectively.(Gum et al., 2009) Another nationally representative study, the Aging, Demographics and Memory Study, reported the prevalence of dementia as 16% and 11% among women and men aged 70 years and older, respectively.(Plassman et al., 2007) Both conditions have been related to several adverse health outcomes including increased disability and mortality.(WHO, 2012; Wolitzky-Taylor et al., 2010)

Multiple lines of evidence support a significant association between anxiety and cognitive impairment. First, cross-sectional studies documented lower cognitive function in older adults with heightened anxiety (Beaudreau & O'Hara, 2009; Bierman et al., 2005; Mantella et al., 2007; Wetherell et al., 2002), and elevated anxiety symptoms in older adults with cognitive impairment.(Andreescu et al., 2014; Geda et al., 2008; Lopez et al., 2003; Lyketsos et al., 2002) Second, longitudinal studies have suggested that anxiety increased the risk of progression of mild cognitive impairment (MCI) to dementia.(Gallagher et al., 2011; Palmer et al., 2007) Third, a number of studies reported that the use of benzodiazepines, a group of anxiolytic medications, was associated with risk of cognitive impairment or decline,(Billioti de Gage et al., 2012; Gallacher et al., 2012; Lagnaoui et al., 2002; Paterniti et al., 2002) This result potentially suggests that benzodiazepine use may be a marker of the underlying condition anxiety, although the possibility remains that the medication themselves impair cognition. (Yaffe & Boustani,

2014) Finally, there is a high co-occurrence between anxiety and depression(Byers et al., 2010; Kessler et al., 2003), which itself is a potential risk factor for cognitive impairment.(Byers & Yaffe, 2011; Ganguli, 2009)

The longitudinal relationship between anxiety and subsequent cognitive impairment in older adults remains unclear.(Beaudreau & O'Hara, 2008) Previous longitudinal research examining this relationship has reported inconsistent findings, and was limited by small sample size, short follow-up, measurement issues and not accounting for important confounders.(Bierman et al., 2008; Burton et al., 2013; Cherbuin et al., 2009; de Bruijn et al., 2014; Gallacher et al., 2009); Okereke and Grodstein (2013); (Pietrzak et al., 2012; Potvin, Forget, et al., 2011; Sinoff & Werner, 2003) Previous studies also did not investigate how specific characteristics, such as severity, of anxiety are related to cognitive impairment.

Anxiety disorders have been shown to have unique influence on men compared to women, and were associated with lower disability (Baxter et al., 2014) but higher mortality.(van Hout et al., 2004) Therefore, it is important to examine the relationship between anxiety and cognitive impairment separately for men and women. We are aware of only one prospective study that examined this issue in older men (Gallacher et al., 2009), and this study included men aged 48 to 67 years and it did not adjust specifically for depression.

In this longitudinal study, we examined the association between presence and severity of generalized anxiety symptoms, and cognitive decline among older men enrolled in the Osteoporotic Fractures in Men (MrOS) Study. We hypothesized that anxiety symptoms will be associated with increased risk of cognitive decline.

5.3 METHODS

5.3.1 Population

We utilized data from the Osteoporotic Fractures in Men (MrOS) Study, a prospective cohort study of community-dwelling men aged 65 years and older.(Orwoll et al., 2005) In brief, 5,994 older men were recruited during 2000-2002 from the following 6 locations in the United States: Birmingham, Alabama; Minneapolis, Minnesota; Monongahela Valley (near Pittsburgh), Pennsylvania; Palo Alto, California; Portland, Oregon; and San Diego, California. Men were excluded if they were unable to walk without assistance or had a bilateral hip replacement. The institutional review board at each site approved the study and participants provided written informed consent.

For this analysis, we used data collected at 3 visits as follows: baseline (2003-2005; MrOS Sleep Visit), visit 2 (2005-2006; MrOS Visit 2) and visit 3 (2007-2009; MrOS Visit 3). From the 3,135 participants at baseline, 3,122 men had complete data on measurements of anxiety and cognitive function. Of the 3,122 men with complete exposure and outcome data, we excluded 162 men with probable cognitive impairment at the baseline, with the following criteria: Modified Mini-Mental State examination (3MS) (Teng & Chui, 1987) score < 80(Kuller et al., 2003) (n = 106), use of dementia medication (n = 44), or both (n = 12). Of the 2,960 cognitively healthy men with complete data, 2,818 men provided data on cognitive function at either visit 2 or visit 3, and thus comprised our analytical sample.

5.3.2 Measurement of anxiety symptoms

At the baseline, anxiety symptoms were measured using the Goldberg Anxiety Scale (GAS).(Goldberg et al., 1988) GAS is a 9-item self-report instrument that inquires about anxiety symptoms experienced in the past month. GAS items span cognitive, affective, and somatic symptoms of anxiety, and are rated as yes (1) or no (0) answers with a total score ranging from 0 to 9. Participants must answer yes to at least 2 of the first 4 items in order to have the subsequent 5 items included in their total score. The 4 screening items are as follows: being keyed up or on edge; worrying a lot; being irritable, and having difficulty relaxing. The recommended cutoff score of 5 suggests that a participant has a 50% chance of a clinically significant anxiety, while higher scores substantially increase the probability of a significant anxiety disturbance. To study the level of anxiety symptoms, we classified participants according to baseline GAS score into the following 3 groups: no anxiety (0), mild anxiety (1-4), and moderate/severe anxiety (5-9).

5.3.3 Measurement of cognitive function

At the Sleep Visit, Visit 2 and Visit 3, two neuropsychological tests were administered to participants: the 3MS and the Trails B.(Reitan & Wolfson, 1985)

The 3MS assesses global cognitive function with components for orientation, concentration, language, praxis, and immediate and delayed memory. The 3MS score ranges from 0 to 100 with higher scores indicating better cognitive function. Cognitive decline in the 3MS is indicated by a negative change, with a lower score at a follow-up measurement. Clinically significant cognitive decline in 3MS was defined as a decline of five points or more between baseline and visit 3.(Andrew & Rockwood, 2008; Blackwell et al., 2014)

The Trails B is primarily a measure of executive function but it also assesses attention, sequencing and visual scanning. This is a timed test with 300 seconds allowed to complete it, with faster completion time indicating better cognitive function. Cognitive decline in the Trails B is indicated by a positive change, with a longer completion time at a follow-up measurement. Clinically significant cognitive decline in Trails B was defined as being in the worst decile of change between baseline and visit 3 (change of ≥ 65 seconds).(Blackwell et al., 2014; Ganguli et al., 1993)

5.3.4 Other measurements

At the Sleep Visit, additional measurements were collected via self-report questionnaires. Demographic information included age, race, and education. Marital status was obtained at visit 2. Medical history was defined as prior physician diagnosis of select medical conditions. Participants reported smoking status, alcohol use, and self-rated health status. Physical activity was assessed using the physical activity scale for the elderly (PASE).(Washburn, Smith, Jette, & Janney, 1993) Functional status was assessed by collecting information on difficulty with 5 instrumental activities of daily living (IADL), which included walking 2 to 3 blocks on level ground, climbing up to 10 steps, preparing meals, doing heavy housework, and shopping for groceries or clothing. The number of activities that were difficult was summed for a total IADL score. The Geriatric Depression Scale (GDS)(Lyness et al., 1997) was used to assess depressive symptoms, with the standard cutoff score of 6 or more to define clinically significant depressive symptoms. The Pittsburgh Sleep Quality Index (PSQI)(Buysse et al., 1989) was used to assess sleep, with the standard cutoff score of 5 or more to define poor sleep. Medication use was ascertained by asking participants to bring all current prescription and non-prescription

medications used in the past month to their clinic visits. Medications were coded and categorized using the Iowa Drug Information Service (IDIS) scheme.(Pahor et al., 1994)

5.3.5 Statistical analysis

We calculated descriptive statistics for all variables and compared participants by level of anxiety symptoms at baseline. For these comparisons, we used chi-squared test (or Fisher's exact test for low expected cell counts) for categorical variables, one-way ANOVA test for normally distributed continuous data and the Kruskal Wallis test for skewed continuous data. Next, we examined the association of anxiety symptoms with baseline and change in 3MS score and time to complete Trails B using repeated measures mixed effects linear regression models. These models take into account the within-subject correlation of repeated measures and the missing data. The models included random intercept and slope of the cognitive measurements over time, assuming an unstructured covariance matrix. Time was modeled as a continuous variable indicating years from baseline. Finally, we examined the association of anxiety symptoms with clinically significant cognitive decline using logistic regression models. We present unadjusted and multivariable-adjusted models. In all models, we adjusted for clinic site, age, depression, poor sleep and psychotropic medications (benzodiazepines, non-benzodiazepine non-barbiturate sedative hypnotics and antidepressants) due to their potential strong confounding effect on the relationship between anxiety and cognitive function. Additional baseline covariates (race, education, marital status, medical co-morbidity, physical activity, alcohol, smoking, self-rated health and IADL impairment) were selected for inclusion in the multivariable models by

manual backward elimination of the least significant variable until all variables were less than p=0.05. All statistical analyses were conducted with Stata version 13.1 (StataCorp LP, College Station, TX, USA).

5.4 RESULTS

5.4.1 Characteristics of participants

Baseline characteristics of participants are presented in Table 5.6.1. At baseline, there were 226 (8%) men who had moderate/severe anxiety symptoms and 690 (24%) who had mild anxiety symptoms. Men with moderate/severe or mild anxiety symptoms at baseline were more likely to have lower level of education, have depressed mood and poor sleep, take more psychotropic medications, suffer from more chronic medical conditions, and have more impairments in daily living activities compared to those with no anxiety symptoms. After mean follow-up time of 3.4 (standard deviation [SD] ±0.5) years, 472 (19%) men had clinically significant decline in global cognitive function and 240 (10%) men had clinically significant decline in executive function. The mean change in the 3MS score was 1.3 (SD ±5.5) points lower and the mean change in the time to complete Trails B was 9.1 (SD ±49.2) seconds longer.

5.4.2 Anxiety symptoms and 3MS test

At baseline, there was a statistically significant difference in 3MS score by level of anxiety symptoms. Those with no anxiety symptoms at baseline had a mean score of 93.80 points versus 93.45 and 92.53 for those with mild and moderate/severe symptoms, respectively ($p<0.001$) (Table 5.6.2). The 3-year 3MS score decline was higher among men with mild anxiety symptoms compared to those with no symptoms or with moderate/severe symptoms (-1.46 points versus -

1.08 and -0.84 respectively, p<0.001). Results were similar in the multivariable-adjusted model (Figure 5.6.1). There was no significant interaction between anxiety symptoms and time (p=0.13).

The association of anxiety symptoms and clinically significant change in the global cognitive outcome is shown in Table 3. Overall, there was no significant association between anxiety symptoms, including mild and more severe symptoms, and clinically significant decline in 3MS.

5.4.3 Anxiety symptoms and Trails B test

At baseline, time to complete Trails B test varied by level of anxiety symptoms. Those with no anxiety symptoms at baseline had a mean test completion time of 114.92 seconds versus 119.36 and 124.42 seconds for those with mild and moderate/severe symptoms, respectively (p=0.01) (Table 5.6.2). The 3-year decline in Trails B test (increase in completion time) was more prominent in men with moderate/severe anxiety symptoms compared to those with no symptoms or with mild symptoms (+15.90 seconds versus +8.27 and +11.80 respectively, p=0.001). In the multivariable-adjusted model, similar pattern of change over time was observed but difference between groups was marginally significant (p= 0.05). In this model, the anxiety groups were not significantly different at baseline (p= 0.42) (Figure 5.6.2). This model showed statistically significant interaction term for anxiety symptoms with time (p=0.04), indicating that over time those with moderate/severe anxiety had faster decline in executive function.

There was a consistent association between anxiety symptoms and clinically significant worsening of Trails B test completion time (Table 5.6.3). In the multivariable-adjusted model, older men with any anxiety symptoms at baseline were 1.40 times more likely to have clinically

significant worsening in Trails B test completion time compared to those without any anxiety symptoms at baseline (OR = 1.40, 95% CI 1.04, 1.88). This relationship was strongest for moderate/severe anxiety symptoms (unadjusted OR = 1.86, 95% CI 1.19, 2.90); however, this association was attenuated in the multivariable-adjusted models.

5.5 DISCUSSION

This prospective study showed that older men with anxiety symptoms experienced greater declines in both global cognitive function and executive function over 3.4 years compared to older men with no anxiety symptoms. The decline reached clinically significant level in executive function but not global cognitive function. These findings are independent of demographic characteristics, depression, poor sleep and psychotropic medications.

Our findings are consistent with prospective studies that reported significant associations between anxiety and cognitive impairment, but extend these findings to show the cognitive domain that may be largely influenced by anxiety in older men is executive function. Prior cross-sectional studies reported an association between anxiety and poor executive function. (Beaudreau & O'Hara, 2009; Bierman et al., 2005; Mantella et al., 2007; Yochim et al., 2013) For instance, Mantella et al. found that older adults with generalized anxiety disorder performed worse on Trails B compared to healthy controls.(Mantella et al., 2007) Our study replicates these findings in a longitudinal design. Our work also is consistent with one prospective study of 1,160 men aged 48 to 67 years that reported an association between high anxiety level and incident cognitive impairment (adjusted OR 2.58, 95% CI 1.11, 5.99).(Gallacher et al., 2009) Our study extends this finding to men aged 65 years and older, while adjusting specifically for depression.

However, it is noteworthy that other prospective studies found significant association between anxiety and clinically significant global cognitive function(Potvin, Forget, et al., 2011; Sinoff & Werner, 2003), but our study did not. Our study as well was not consistent with other

prospective studies that found no association between anxiety and cognitive impairment in older adults.(Bierman et al., 2008; Cherbuin et al., 2009; de Bruijn et al., 2014)

The literature suggests three possibilities to explain the relationship between anxiety and cognitive decline. First, anxiety could be a risk factor for cognitive decline. To support this etiological hypothesis, a dose-response relationship is to be expected, where increasing level of anxiety symptoms will be associated with increasing level of cognitive decline. Our findings showed that mild and moderate/severe levels of anxiety had contrasting relationship with cognitive function, and as such our study does not support this hypothesis. This is based on an assumption that both levels of anxiety symptoms and cognitive domains reflect similar pathological processes across levels, which cannot be confirmed or ruled out by our measurements. Second, the association between anxiety and cognitive decline could be explained by shared risk factors, such as depression. It is noteworthy that about 30% of men with moderate/severe anxiety in our study reported clinically significant depressive symptoms. However, we adjusted our models for depression and other important potential confounders, and therefore this hypothesis is less likely to explain our findings. Third, anxiety could be a consequence of cognitive decline. Severe cognitive impairment, such as dementia, is a degenerative disease with a long prodromal period, and thus it is plausible that anxiety may appear as an early symptom or as a reaction to subtle cognitive deficits before developing significant cognitive impairment. Our follow-up duration of 3.4 years may have been too short to show a clinically significant decline in global cognitive function. The small but varying influence of anxiety symptoms level on global cognitive function and executive functioning may reflect clinical and pathological heterogeneity that stirred anxiety symptoms to present differently.

Strengths of this study include the prospective cohort design, a large, well-characterized cohort of older community-dwelling men, and consideration of a large number of possible confounders. Our study has several limitations. First, our sample was comprised of mostly Caucasian older men, and our results may not be generalizable to younger men, other ethnic groups or women. Second, anxiety symptoms were self-reported without clinical assessment and were measured by an instrument that was developed in young adults. However, GAS has shown moderate validity in a sample of older adults.(Pachana et al., 2007) Third, our measures of cognitive function were limited to measures of global cognitive function and executive function. Fourth, we excluded participants with probable cognitive impairment at baseline using established criteria for cognitive impairment. However, we did not have clinical assessments and therefore our sample may have included participants with subtle cognitive impairment. Finally, we could not control for residual confounding inherent in the observational design of the study.

Our findings suggest that anxiety symptoms in cognitively healthy older men may serve as an important predictor of future risk of decline in executive functioning. This finding is independent of depression, poor sleep, use of psychotropic medications and other important confounders. Future studies should explore potential underlying biological mechanisms linking anxiety symptoms to cognitive decline in older men.

5.6 TABLES AND FIGURES

Table 5.1 Characteristics of participants according to level of anxiety symptoms at baseline

Characteristics	Total N = 2,818	Anxiety symptoms, n (%)			p-value
		No symptoms 1,902 (68)	Mild (1-4 symptoms) 690 (24)	Moderate/Severe (5-9 symptoms) 226 (8)	
Demographics					
Age, years, mean ± SD	76.1 ± 5.3	76.1 ± 5.3	76.0 ± 5.4	75.8 ± 5.4	0.5
Non-Caucasian race, n (%)	221 (7.8)	150 (7.9)	51 (7.4)	20 (8.9)	0.8
High school or less, n (%)	561 (19.9)	357 (18.8)	147 (21.3)	57 (25.2)	0.04
Married, n (%)	2,286 (81.2)	1,543 (81.3)	566 (82.0)	177 (78.3)	0.5
Medical history					
Stroke, n (%)	103 (3.7)	61 (3.2)	30 (4.4)	12 (5.3)	0.15
Parkinson`s disease, n (%)	31 (1.1)	16 (0.8)	8 (1.2)	7 (3.1)	0.01
Myocardial infarction, n (%)	467 (16.6)	294 (15.5)	121 (17.5)	52 (23.0)	0.01
Hypertension, n (%)	1,387 (49.2)	883 (46.4)	369 (53.5)	135 (59.7)	<0.001
Chronic obstructive pulmonary disease, n (%)	141 (5.0)	80 (4.2)	40 (5.8)	21 (9.3)	<0.01
Diabetes, n (%)	364 (12.9)	227 (11.9)	100 (14.5)	37 (16.4)	0.06
Osteoarthritis, n (%)	656 (23.3)	392 (20.6)	175 (25.4)	89 (39.4)	<0.001
Co-morbid conditions, n (%)					<0.001
0	842 (29.9)	630 (33.1)	169 (24.5)	43 (19.0)	
1-2	1,733 (61.5)	1,137 (59.8)	452 (65.5)	144 (63.7)	
3+	243 (8.6)	135 (7.1)	69 (10.0)	39 (17.3)	
Life style					
Physical Activity Scale for the Elderly score, mean ± SD	148.6 ± 71.3	148.4 ± 70.1	153.7 ± 74.2	134.7 ± 70.4	<0.01
Alcoholic drinks per week, mean ± SD	2.9 ± 1.3	2.9 ± 1.2	3.0 ± 1.3	2.7 ± 1.3	0.02
Smoking status					0.4
Never, n (%)	1,124 (39.9)	772 (40.6)	270 (39.1)	82 (36.3)	
Past, n (%)	1,636 (58.0)	1,092 (57.4)	408 (59.1)	136 (60.2)	
Current, n (%)	58 (2.1)	38 (2.0)	12 (1.8)	8 (3.5)	
Quality of life					
Self-rated health status, good/excellent, n (%)	2,466 (87.5)	1,732 (91.1)	598 (86.7)	136 (60.2)	<0.001
Any IADL impairment, n (%)	544 (19.3)	310 (16.3)	145 (21.0)	89 (39.4)	<0.001
Pittsburgh Sleep Quality Index > 5, n (%)	1,208 (42.9)	653 (34.3)	366 (53.0)	189 (83.6)	<0.001
Geriatric Depression Scale ≥ 6, n (%)	155 (5.5)	29 (1.5)	59 (8.6)	67 (29.8)	<0.001
Psychotropic medications					
Benzodiazepine use, n (%)	117 (4.2)	57 (3.0)	30 (4.4)	30 (13.3)	<0.001
Non-benzodiazepine non-barbiturate sedative hypnotic use, n (%)	60 (2.1)	31 (1.6)	17 (2.5)	12 (5.3)	<0.01

Table 5.1 Continued

Any antidepressant use, n (%)	192 (6.8)	96 (5.1)	52 (7.6)	44 (19.5)	<0.001
SSRI antidepressant use n (%)	102 (3.6)	52 (2.7)	27 (3.9)	23 (10.2)	<0.001
TCA antidepressant use, n (%)	37 (1.3)	20 (1.1)	9 (1.3)	8 (3.5)	0.01

Table 5.2 Unadjusted mean baseline and 3-year change in cognitive function by anxiety symptoms at baseline

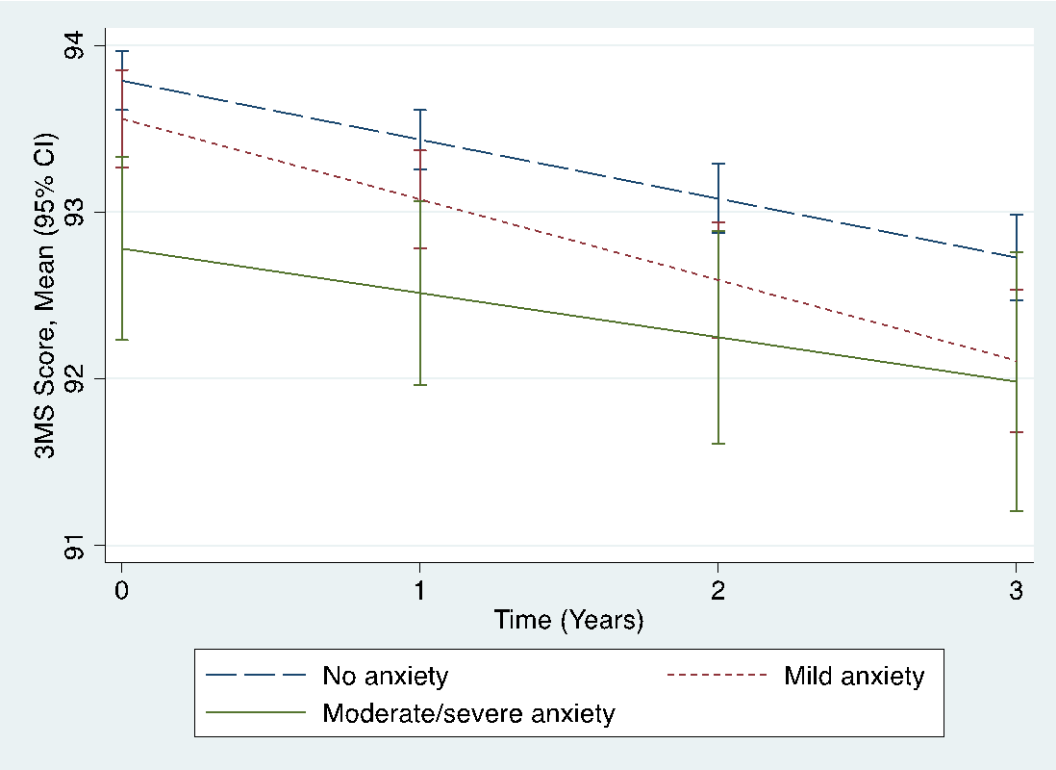
	Anxiety symptoms	Baseline 3MS score	3MS score 3-year change	Baseline time to complete Trails B	Time to complete Trails B 3-year change
Model 1	Any	93.23	-1.31	120.61	+12.81
	None	93.80	-1.08	114.92	+8.27
	p-value	0.001	0.001	0.01	0.001
Model 2	Moderate/severe	92.53	-0.84	124.42	+15.90
	Mild	93.45	-1.46	119.36	+11.80
	None	93.80	-1.08	114.92	+8.27
	p-value	<0.001	<0.001	0.01	0.001

Table 5.3 Association between anxiety symptoms and clinically significant cognitive decline

	Anxiety symptoms	3MS score decline of five points or more		Trails B worst decile of change	
		Unadjusted	Multivariable-adjusted*	Unadjusted	Multivariable-adjusted**
		Odds ratio (95% confidence interval)			
Model 1	Any	1.12 (0.91, 1.39)	1.07 (0.85, 1.35)	1.56 (1.19, 2.05)	1.40 (1.04, 1.88)
	None	1.00 (reference)			
Model 2	Moderate/severe	0.99 (0.67, 1.46)	0.80 (0.51, 1.25)	1.86 (1.19, 2.90)	1.35 (0.81, 2.27)
	Mild	1.17 (0.93, 1.47)	1.14 (0.89, 1.46)	1.47 (1.09, 1.99)	1.41 (1.03, 1.93)
	None	1.00 (reference)			

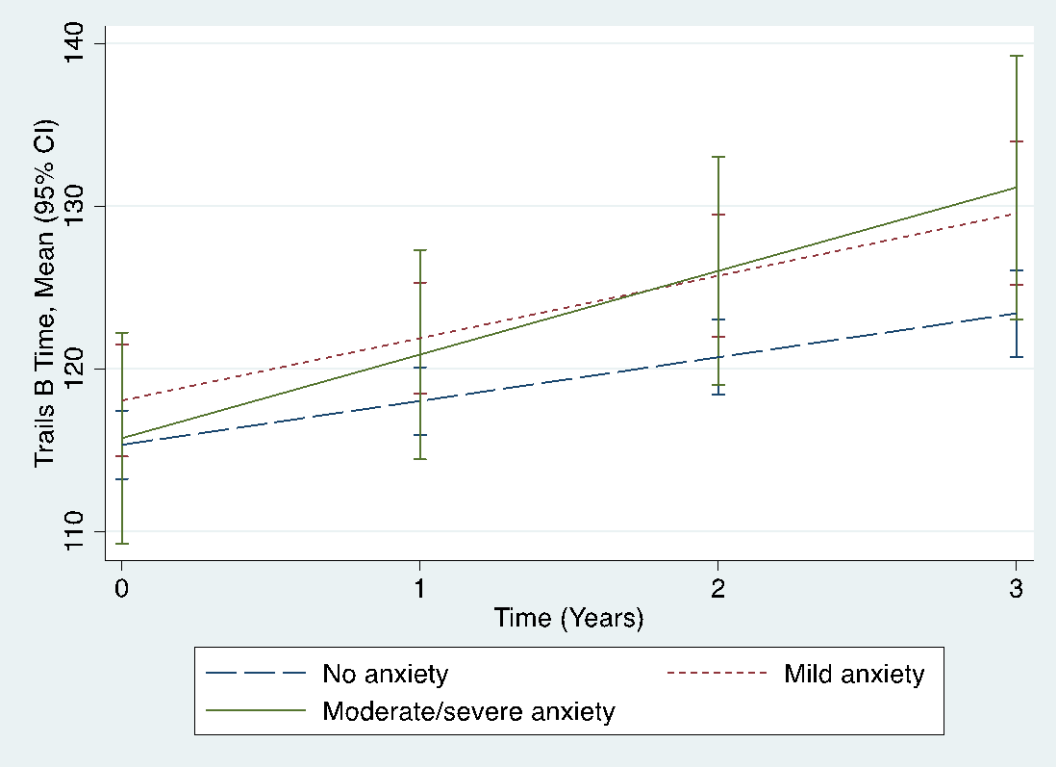
*Models are adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race, education, marital status and IADL impairments.

**Models are adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race and IADL impairments.



*Model is adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race, education, marital status and IADL impairments. [baseline p= <0.01, change p= <0.01]

Figure 5.1 Multivariable-adjusted 3MS score by anxiety groups



*Model is adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race, education, marital status and IADL impairments. [baseline p= 0.42, change p= 0.05]

Figure 5.2 Multivariable-adjusted Trails B time by anxiety group

6.0 DISCUSSION

6.1 SUMMARY, CONCLUSIONS AND FUTURE RESEARCH

The primary aim of this dissertation was to investigate anxiety symptoms in older adults with a focus on medications that are used to manage anxiety and impact of anxiety on future cognitive functioning. The aim of the first paper was to investigate the trend of anxiolytic and antidepressant medications use in older community-dwelling men and women, and to explore gender-specific predictors of use of these medications over time. We found that the use of anxiolytic and antidepressant medications increased in this aging cohort over ten years with higher prevalence in women than men. We also found that some predictors of anxiolytic and antidepressant medications use were common among men and women, while some predictors were potentially gender-specific. To our knowledge, this is the first longitudinal study that explored gender-specific predictors of anxiolytic and antidepressant medications use in older adults in the United States. The aim of the second paper was to investigate the relationship between presence, level and changes in anxiety symptoms, and risk of future dementia, MCI and decline in cognitive functioning among the oldest old community-dwelling women. We found that mild anxiety symptoms in oldest old women were associated with increased odds of incident dementia over five years. We also found that change in anxiety symptoms over time, as denoted by incident and receded anxiety symptoms, was associated with increased risk of dementia. We

did not observe an association between anxiety symptoms and MCI. To our knowledge, this is the first longitudinal study that explored the relationship between anxiety symptoms and cognitive impairment in the oldest old women in the United States. The aim of the third paper was to investigate the relationship between presence and level of anxiety symptoms, and risk of future cognitive decline among older community-dwelling men. We found that anxiety symptoms in older men were associated with greater declines in both global cognitive function and executive function over three years. We also found that such a decline reached clinically significant level in executive function but not global cognitive function. To our knowledge, this is the first longitudinal study that explored the relationship between anxiety symptoms and cognitive decline in older men in the United States.

Taken together, these findings highlight the importance of anxiety symptoms in older adults. Our finding that anxiolytic and antidepressant medications use in older adults was increasing may indicate either new reporting of previously undertreated condition or inappropriate use of these medications. Both possibilities are alarming given the greater morbidity and mortality associated with a condition such as anxiety and the increased vulnerability of older adults to psychotropic medications. Our finding that mild but not moderate/severe anxiety symptoms were associated with dementia but not with MCI may reflect unique pathological profiles, which presented by varying level of anxiety symptoms. Similarly, our finding that anxiety symptoms were associated with clinically significant decline in executive functioning but not in global cognitive functioning may also point toward clinical and pathological heterogeneity. This is critical for better understanding of the nature of the relationship between anxiety and cognitive impairment. Our findings regarding anxiety symptoms and subsequent cognitive impairment suggest that anxiety is likely an early symptom

or a reaction to subtle cognitive deficits before the occurrence of significant cognitive impairment. However, these findings do not completely rule out the possibility that anxiety may be a potential risk factor for cognitive impairment as they may be specific to our samples. Finally, our findings from the three papers extend the literature specific to older men and women and emphasize the importance of considering men and women separately when studying late-life anxiety.

Thus, future studies should explore the determinants of anxiety symptoms in older men and women, especially the oldest old. Additionally, future studies should investigate determinants of prescribing of anxiolytic medications by healthcare providers and whether this varies by gender of the older patient. Future research should also explore potential underlying biological pathways that may link anxiety symptoms to cognitive impairment that are specific to older men or women. Due to heterogeneity of anxiety and cognitive impairment, future studies should examine how specific characteristics of anxiety, such as level, changes and type, are related to different domains and levels of cognitive impairment. Finally, changes over time of potential confounders of the relationship between anxiety and cognitive impairment, such as depression and psychotropic medications, should be taken into account in future studies.

6.2 PUBLIC HEALTH IMPLICATIONS

Worldwide, anxiety disorders are the sixth leading cause of all years of life lived with disability, ahead of diabetes, cancers and stroke. (Baxter et al., 2014) In the United States, anxiety disorders are the most common mental disorders among older adults, with a lifetime prevalence of 16.6% among women and 9.6% among men aged 65 years and older. (Gum et al., 2009) Symptoms and disorders of anxiety in older adults have been associated with increased risk of disability and mortality. (Wolitzky-Taylor et al., 2010) Further, it is well documented that anxiety in older adults is co-morbid with psychiatric conditions, including depression, medical conditions, including cardiovascular disease, and cognitive impairment, including Alzheimer's disease.(Wolitzky-Taylor et al., 2010) Therefore, management of anxiety symptoms and disorders in older adults will have significant implications for public health. In addition to reducing suffering experienced by patients with anxiety, treating anxiety has the potential to prevent developing other burdensome conditions, such as cognitive impairment, and reduce disability and mortality. Thus, findings from this research will help in understanding the role of anxiety as a predictor of future cognitive impairment and whether anxiety can early identify those at higher risk or it is a potentially modifiable risk factor. While pharmacotherapy is effective in managing anxiety disorders, it bears its risks in older adults. Thus, findings from this research will inform future intervention research that target older users of anxiety-related medications.

APPENDIX A

TABLE OF LONGITUDINAL STUDIES

Table 6.1 Longitudinal studies that investigated the association between generalized anxiety and cognitive impairment in older adults

Author (year)	Country	Sample	Follow-up, years	Exposure measure	Outcome measure	Adjusted covariates	Main findings
Sinoff and Werner (2003)	Israel	137 older adults, 78.9 years mean age, 27% lost to follow-up	3.1 (mean)	Anxiety symptoms (Sinoff's Short Anxiety Screening Test, score ≥24)	Cognitive impairment (Mini-Mental State Examination, score <24)	Age, gender, education, marital status, depression, loss of memory complaint	Those suffering of anxiety had higher risk for developing cognitive impairment (adjusted relative risk = 3.96, 95% confidence interval 1.69, 9.08)
Bierman et al. (2008)	Netherlands	2,351 older adults, 69.5 years mean age, 53.5% female, 37.5% lost to follow-up	9	Anxiety symptoms (Hospital Anxiety and Depression Scale)	Cognitive decline (Mini-Mental State Examination, Raven's Colored Progressive Matrices, Rey Auditory Verbal Learning Test	Age, gender, education, alcohol, benzodiazepine, number of chronic diseases, depression	Previous measurement of anxiety symptoms was not associated with cognitive decline at a later time point
Cherbuin et al. (2009)	Australia	2,083 older adults, 62.4 years mean age, 13% lost to follow-up	4	Anxiety symptoms (Goldberg Anxiety Scale)	Mild cognitive impairment, mild cognitive disorder (clinical diagnosis)	Age, gender, education, body mass index, blood pressure, forced vital capacity, visual acuity, arthritis,	Anxiety symptoms were not associated with mild cognitive impairment or mild cognitive

Table 6.1 Continued

						diabetes, physical health self-report, mental health self-report, depression, smoking, alcohol, APOE, medications (blood pressure, cholesterol, anxiety, depression)	disorder. Taking anxiety medications was only associated with mild cognitive impairment in a model adjusted for age, gender and education (odds ratio = 4.08, 95% confidence interval 1.16, 14.39)
Gallacher et al. (2009)	United Kingdom	1,160 older men, 56.1 years mean age, 20% lost to follow-up	17.3 (mean)	Anxiety symptoms (State Trait Anxiety Inventory, 31st-95th centile)	Dementia, cognitive impairment not dementia, (clinical adjudication, DSM-IV criteria)	Age, social class, marital status, smoking, alcohol, blood pressure, body mass index, cholesterol, previous vascular disease, psychological distress, premorbid cognitive function	High anxiety level was associated with any cognitive impairment (adjusted odds ratio 2.58, 95% confidence interval 1.11, 5.99) and with cognitive impairment not dementia (adjusted odds ratio = 2.98, 95% confidence interval 1.20, 7.38)
Potvin, Forget, et al. (2011)	Canada	1,942 older adults, 74.3 years mean age, 20.5% lost to follow-up	1	Anxiety disorders, symptoms (clinical diagnosis, DSM-IV criteria)	Cognitive Impairment (Mini-Mental State Examination, score <15th percentile)	Age, education, gender, living area, cognitive score at baseline, psychotropic drugs, brain disorders, cardiovascular conditions, number of chronic diseases, depression	In men, anxiety disorders but not symptoms were associated with cognitive impairment (adjusted odds ratio = 6.27, 95% confidence interval 1.39, 28.29). In women, anxiety symptoms but not disorders were associated with cognitive impairment (adjusted odds ratio = 2.14, 95% confidence interval 1.06, 4.34)
Pietrzak	Australi	263 older	2	Pathologic worry	Cognitive decline	Age, depression	Mildly elevated

Table 6.1 Continued

et al. (2012)	a	adults, 61.6 years mean age, 71.1% female, 25.9% lost to follow-up		(Penn State Worry Questionnaire, median split into mildly elevated worry and minimal worry groups)	(CogState 6-task test battery)		worry was associated with decline in a test of visual learning and memory (adjusted odds ratio = 3.83, 95% confidence interval 1.03, 14.28)
Burton et al. (2013)	United Kingdom	400 dementia cases (81.40 years mean age, 62% female), 1353 controls (80.87 years mean age, 63% female)	Case-control study period: 2000-2008	Anxiety diagnosis (primary care records)	Dementia diagnosis (primary care records)	Age, gender, practice, year of case diagnosis of dementia, hypertension, ischemic heart disease, cerebrovascular disease, hypotension, dyslipidaemia, diabetes, depression	Past anxiety diagnosis was associated with a future dementia diagnosis (adjusted odds ratio = 2.67, 95% confidence interval 2.01, 3.54). Having anxiety diagnosis alone was associated with dementia diagnosis in men (adjusted odds ratio = 3.12, 95% confidence interval 1.78, 5.47) but not in women
Okereke and Grodstein (2013)	United States	16,351 older women, 63 years mean age	4.4 years (mean)	Phobic anxiety symptoms (Crowne-Crisp Index; 0-1, 2, 3, 4, 5 and 6-16)	Cognitive decline (Telephone Interview for Cognitive Status [TICS], East Boston Memory Test, category fluency test, TICS delayed 10-word recall, digit span backward)	Age, education level, cigarette smoking, current postmenopausal hormone use, hypertension, diabetes, elevated cholesterol, heart disease, body mass index, alcohol intake, physical activity level and depression	There were no relations between phobic anxiety and subsequent cognitive change
de Bruijn et al. (2014)	Netherlands	Sample 1: 2,708 older adults, 68.6 years mean age, 55% female Sample 2: 3,069 older adults, 75.5	Sample 1: 11.8 (mean) Sample 2: 5.8 (mean)	Sample 1: anxiety symptoms (Hospital Anxiety and Depression Scale, score ≥ 8) Sample 2: anxiety disorders	Dementia (clinical adjudication, DSM-III-R criteria), cognitive decline (Letter-Digit Substitution Task, Stroop Test, Verbal Fluency Test,	Age, gender, education, APOE, depression	No association between anxiety symptoms or disorders with risk of dementia

Table 6.1 Continued

		years mean age, 59% female		(Composite International Diagnostic Interview)	Verbal Learning Test)		
Geda et al. (2014)	United States	1,587 older adults, 79.3 years median age, 50% female	5 (median)	Anxiety symptom (Neuropsychiatric Inventory Questionnaire)	Mild cognitive impairment (clinical adjudication, Mayo Clinic criteria)	Age, gender, education, medical comorbidity	Anxiety significantly predicted incident mild cognitive impairment (hazard ratio = 1.87, 95% confidence interval1.28, 2.73)
Zilkens et al. (2014)	Australia	13, 568 dementia cases aged 65 to 84 years were sex- and age-matched to a control	Case-control study period: 1966-2009	Anxiety disorder diagnosis (administrative health records)	Dementia diagnosis (administrative health records)	Diabetes, heart disease, cerebrovascular disease and smoking	Past anxiety disorder diagnosis was associated with future dementia diagnosis (adjusted odds ratio = 1.37, 95% confidence interval 1.14, 1.65)
Pietrzak et al. (2015); Pietrzak et al. (2014)	Australia	333 older adults, 70 years mean age, 50% with subjective memory complaints and 50% APOE ε4 carriers	4.5	Hospital Anxiety and Depression Scale, elevated symptoms (> median score of 4), clinically meaningful anxiety (score ≥ 8)	Cognitive function: verbal memory composite score, visual memory composite score, executive function composite score, language composite score, attention composite score, visuospatial composite score and global cognition score.	Age, educational level, IQ, APOE genotype, subjective memory complaints, number of vascular risk factors, depression	Baseline elevated anxiety symptoms were associated with lower overall global cognition score, and greater decline in global cognition and verbal memory over time.

APPENDIX B

GOLDBERG ANXIETY SCALE ITEMS RESPONSES

Table 6.2 Positive responses to items in the Goldberg Anxiety Scale in SOF and MrOS

Goldberg Anxiety Scale items, "Yes" response, n (%)	SOF sample N = 1,425	MrOS sample N = 2,818
Have you felt keyed up or on edge?	365 (25.61)	501 (17.78)
Have you been worrying a lot?	315 (22.11)	360 (12.78)
Have you been irritable?	188 (13.19)	471 (16.71)
Have you had difficulty relaxing?	250 (17.54)	306 (10.86)
Have you been sleeping poorly?	486 (34.13)	659 (23.39)
Have you had headaches or neck aches?	399 (28.00)	550 (19.52)
Have you had any of the following: trembling, tingling, dizzy spells, sweating, frequency, diarrhea?	540 (37.89)	782 (27.76)
Have you been worried about your health?	299 (20.98)	458 (16.25)
Have you had difficulty falling asleep?	448 (31.46)	462 (16.39)

APPENDIX C

FACTOR ANALYSIS FOR PAPER 2

Table 6.3 Profiles of anxiety symptoms in the SOF sample

Goldberg Anxiety Scale items	*Factor 1 "Worry profile" 31% variance	*Factor 2 "Sleep profile" 23% variance	*Factor 3 "Somatic profile" 17% variance
Have you felt keyed up or on edge?	X		
Have you been worrying a lot?	X		
Have you been irritable?	X		
Have you had difficulty relaxing?	X	X	
Have you been sleeping poorly?		X	
Have you had headaches or neck aches?			X
Have you had any of the following: trembling, tingling, dizzy spells, sweating, frequency, diarrhea?			X
Have you been worried about your health?	X		X
Have you had difficulty falling asleep?		X	

*****Based factor loadings > 0.30 with Varimax rotation and using a polychoric correlation matrix.

Table 6.4 Association between profiles of anxiety symptoms and dementia and mild cognitive impairment

Profiles of anxiety symptoms	Dementia**		Mild cognitive impairment**	
	Unadjusted	Multivariable-adjusted*	Unadjusted	Multivariable-adjusted*
	Odds ratio (95% confidence interval)			
Worry	1.64 (1.10, 2.45)	1.50 (0.89, 2.53)	1.17 (0.82, 1.68)	1.24 (0.79, 1.94)
Sleep	0.81 (0.58, 1.13)	0.76 (0.47, 1.23)	0.89 (0.66, 1.18)	0.90 (0.61, 1.34)
Somatic	1.12 (0.80, 1.56)	0.84 (0.55, 1.28)	1.10 (0.83, 1.47)	0.86 (0.61, 1.22)

*Models are adjusted for demographics (age, education and marital status), health behaviors (smoking, alcohol use and exercise), medical history (hypertension, myocardial infarction, stroke, and diabetes), psychotropic medications (benzodiazepine, non-benzodiazepine non-barbiturate sedative hypnotic and antidepressant), depression and poor sleep.

**Reference group: normal cognition.

APPENDIX D

FACTOR ANALYSIS FOR PAPER 3

Table 6.5 Profiles of anxiety symptoms in the MrOS sample

Goldberg Anxiety Scale items	*Factor 1 "Worry profile" 31% variance	*Factor 2 "Sleep profile" 22% variance	*Factor 3 "Somatic profile" 18% variance
Have you felt keyed up or on edge?	X		
Have you been worrying a lot?	X		
Have you been irritable?	X		
Have you had difficulty relaxing?	X	X	
Have you been sleeping poorly?		X	
Have you had headaches or neck aches?			X
Have you had any of the following: trembling, tingling, dizzy spells, sweating, frequency, diarrhea?			X
Have you been worried about your health?	X		X
Have you had difficulty falling asleep?		X	

*****Based factor loadings > 0.30 with Varimax rotation and using a polychoric correlation matrix.

Table 6.6 Association between profiles of anxiety symptoms and cognitive decline

Profiles of anxiety symptoms	3MS score decline of five points or more		Trails B worst decile of change	
	Unadjusted	Multivariable-adjusted*	Unadjusted	Multivariable-adjusted**
	Odds ratio (95% confidence interval)			
Worry	1.05 (0.76, 1.44)	0.98 (0.68, 1.41)	1.79 (1.22, 2.63)	1.58 (1.02, 2.45)
Sleep	1.25 (0.96, 1.63)	1.22 (0.88, 1.69)	1.35 (0.96, 1.90)	1.11 (0.74, 1.68)
Somatic	1.51 (1.19, 1.92)	1.32 (1.01, 1.73)	1.86 (1.37, 2.54)	1.58 (1.12, 2.22)

*Model is adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race, education, marital status and IADL impairments.

**Model is adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race and IADL impairments.

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