Title

Anxiety symptoms and risk of dementia and mild cognitive impairment in the oldest old women

Journal

Aging & Mental Health, 22(4)

ISSN

1360-7863

Authors

Kassem, Ahmed M
Ganguli, Mary
Yaffe, Kristine
et al.

Publication Date

2018-04-03

DOI

10.1080/13607863.2016.1274370

Peer reviewed

Published in final edited form as:

Aging Ment Health. 2018 April ; 22(4): 474–482. doi:10.1080/13607863.2016.1274370.

Anxiety symptoms and risk of dementia and mild cognitive impairment in the oldest old women

Ahmed M. Kassem, MBBCh, MPH, PhD[1], **Mary Ganguli, MD, MPH**[1,2], **Kristine Yaffe, MD**[3], **Joseph T. Hanlon, PharmD, MS**[1,4], **Oscar L. Lopez, MD**[2], **John W. Wilson, PhD**[5], **Kristine Ensrud, MD, MPH**[6], and **Jane A. Cauley, DrPH**[1] **for the Study of Osteoporotic Fractures (SOF) Research Group**

[1]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, United States

[2]Departments of Psychiatry and Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15261, United States

[3]Departments of Psychiatry, Neurology and Epidemiology, University of California, San Francisco, CA 94143, United States

[4]Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15261, United States

[5]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, United States

[6]Department of Medicine and Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN 55417, United States

Abstract

Objectives—Research is limited and findings conflict regarding anxiety as a predictor of future cognitive decline in the oldest old persons. We examined the relationship between levels of and changes in anxiety symptoms, and subsequent dementia and mild cognitive impairment (MCI) in the oldest old women.

Method—We conducted secondary analyses of data collected from 1,425 community-dwelling women (mean age = 82.8, SD ±3.1 years) followed on average for five 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, or use of dementia medication) at baseline were excluded.

Results—At baseline, 190 (13%) women had moderate/severe anxiety symptoms and 403 (28%) 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 with those with no anxiety symptoms. Compared

Corresponding Author: Jane A. Cauley, DrPH, 130 DeSoto Street, A510 Crabtree Hall, Pittsburgh, PA 15261, USA. jcauley@edc.pitt.edu, Tel: 412-624-3057, Fax: 412-624-7397.

No Disclosures to Report.

with those with no anxiety symptoms at baseline, women with mild anxiety symptoms were more likely to develop dementia at follow-up (multivariable-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 anxiety symptoms may predict future risk of dementia, but not MCI. Future studies should explore potential biological mechanisms underlying associations of anxiety with cognitive impairment.

Keywords

aging; epidemiology; community sample

Introduction

In the United States, a nationally representative survey, the National Comorbidity Survey Replication, has 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, King-Kallimanis, & Kohn, 2009). Another nationally representative study, the Aging, Demographics and Memory Study, has reported the prevalence of dementia as 15.7% and 11.1% among women and men aged 70 years and older, respectively (Plassman et al., 2007). Both conditions are related to several adverse health outcomes, including increased disability and mortality (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014; Mehta et al., 2003; van Hout et al., 2004; World Health Organization, 2012).

Multiple lines of evidence support a significant association between these conditions. First, cross-sectional studies have documented lower cognitive function in older adults with anxiety disorders or heightened anxiety symptoms (Beaudreau & O'Hara, 2009; Bierman, Comijs, Jonker, & Beekman, 2005; Mantella et al., 2007; Wetherell, Reynolds, Gatz, & Pedersen, 2002). It is worth noting that the lower cognitive function in these studies does not necessarily indicate cognitive disorder. Other cross-sectional studies have documented higher 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 symptoms 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 have reported that use of benzodiazepines, a class of anxiolytic medications, was associated with elevated risk of cognitive decline or impairment (Billioti de Gage et al., 2012; Gallacher et al., 2012; Lagnaoui et al., 2002; Paterniti, Dufouil, & Alperovitch, 2002). This association may, however, reflect confounding by indication: benzodiazepine use is a marker of an underlying anxiety disorder that could be the true predictor of cognitive impairment (Yaffe & Boustani, 2014). Finally, there is a high co-occurrence of anxiety with depression (Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010; Kessler et al., 2003), which itself is a potential risk factor for cognitive impairment (Byers & Yaffe, 2011; Ganguli, 2009; Zeki Al Hazzouri et al., 2014). This co-occurrence may indicate some overlap in the underlying etiology that links anxiety and depression with cognitive impairment. Therefore, it is crucial to consider both conditions when investigating their independent effect, if any, on cognitive impairment.

Despite these lines of evidence, the longitudinal relationship between anxiety symptoms or disorders, and subsequent cognitive impairment in older adults remains unclear (Beaudreau & O'Hara, 2008). Previous research examining this relationship has been inconclusive, being limited by small sample size, short follow-up, measurement issues, and failure to account for key confounders (Bierman, Comijs, Rijmen, Jonker, & Beekman, 2008; Burton, Campbell, Jordan, Strauss, & Mallen, 2013; Cherbuin et al., 2009; de Bruijn et al., 2014; Gallacher et al., 2009; Okereke & Grodstein, 2013; Pietrzak et al., 2012; Potvin, Forget, Grenier, Preville, & Hudon, 2011; Sinoff & Werner, 2003). Hence, more research is needed to clarify whether anxiety is a potential modifiable risk factor for cognitive impairment, or is an early marker of those who will develop cognitive impairment. Research is needed as well to investigate the relationship between specific characteristics of anxiety symptoms, and mild cognitive impairment and dementia.

As stated earlier, prevalence estimates of anxiety disorders and dementia are higher in women than in men. Female sex is the most consistent correlate and risk factor for anxiety symptoms and disorders (Byers et al., 2010; de Beurs et al., 2001). Women with anxiety have higher disability compared to men (Baxter et al., 2014) and men with anxiety appear to have higher mortality compared to women (van Hout et al., 2004). These findings may reflect unique pathophysiological profiles in men and women due to biological, environmental or cultural differences. Thus, it is appropriate to investigate anxiety separately among women and men. Further, it will be valuable to explore the relationship between anxiety symptoms or disorders, and cognitive impairment in the oldest old persons (aged 80 years or over), which constitutes the fastest growing segment of the population globally (United Nations, 2015). The role of anxiety in development of cognitive impairment in the oldest old may differ than in younger ages, due to distinct social, behavioral, and biological factors that determine survival into very old age (Yaffe et al., 2011).

In this longitudinal study, we examined the association between presence and levels of anxiety symptoms, and risk of subsequent dementia, MCI and decline in cognitive function in a cohort of oldest old women, analyzing secondary data from the Study of Osteoporotic Fractures (SOF). We hypothesized that severe anxiety symptoms at baseline will be positively associated with increased risk of dementia, MCI and decline in cognitive function at follow-up. We also performed exploratory analyses to examine how changes in anxiety symptoms over time could be related to cognitive impairment.

Method

Participants

We performed secondary data analysis utilizing data from SOF (Cummings et al., 1995), a prospective cohort study of community-dwelling women aged 65 years and older. SOF had originally focused on risk factors for fractures and falls but evolved over the years to investigate various determinants of healthy aging. It should be noted that the SOF cohort was not composed of women with osteoporotic fractures, but rather recruited women who might develop such fractures in the future. Therefore, SOF had broad eligibility criteria that were unrelated to osteoporosis as follows: women aged 65 years and older who were able to walk without assistance and had not previously undergone a bilateral hip replacement. In

total, 9,704 predominantly Caucasian older women were initially recruited into SOF from mailings to age-eligible women identified from community-based listings, such as memberships of large health maintenance organizations, in four locations in the United States as follows: Baltimore, Maryland; Minneapolis, Minnesota; Monongahela Valley (near Pittsburgh), Pennsylvania, and Portland, Oregon. Starting with the initial visit (SOF visit 1; 1986–1988), participants attended clinic visits approximately every two to four years. An additional 662 African-American older women were recruited during SOF visit 6 (1997–1998). The institutional review board for protection of human subjects at each study site approved the study and participants provided written informed consent.

For the present analysis, SOF visit 8 (2002–2004), when anxiety was assessed for the first time, served as the baseline visit and SOF visit 9 (2006–2008), when a comprehensive cognitive assessment was performed, served as the follow-up visit. At SOF visit 9, 1,513 women from three of the four original SOF sites underwent the cognitive assessment; thus, only participants from those three sites were included in this study. We included 1,470 women who had anxiety assessment at SOF visit 8 (baseline) and had cognitive status assessment at SOF visit 9 (follow-up). Of these 1,470 women, we excluded 17 women with indeterminate cognitive status at follow-up. We additionally excluded 28 women with probable cognitive impairment at baseline, determined using 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, 30-point) (Folstein, Folstein, & McHugh, 1975) score <24 (n = 19). The remaining 1,425 women constituted the main analytic sample for our study (Figure 1).

The secondary analyses reported here are restricted to existing data on the instruments measuring anxiety, depression, and cognition that were selected by the original investigators of SOF (Spira, Stone, Beaudreau, Ancoli-Israel, & Yaffe, 2009; Yaffe et al., 2011). Potential limitations of these measurement tools are addressed in the Discussion.

Measurement of anxiety symptoms

At the baseline and the follow-up visits, anxiety symptoms were measured using the Goldberg Anxiety Scale (GAS) (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988). GAS is a nine-item self-report instrument that inquires about anxiety symptoms experienced in the past month. GAS items span several anxiety symptoms, and responses are rated as yes (1) or no (0) with a total score ranging from zero to nine. Participants must answer affirmatively to at least two of the first four items in order to have the responses to all nine items included in their total score; otherwise only the responses to the first four items are included. The four screening items are as follows: being keyed up or on edge; worrying a lot; being irritable; and having difficulty relaxing. A cutoff score of five, as recommended by Goldberg et al. (1988), suggests that a participant has a 50% chance of a “clinically important disturbance” of anxiety and higher scores suggest a substantially higher probability that a participant has an anxiety disorder.

To study the levels of anxiety symptoms, we classified participants according to GAS score at baseline into the following three groups, using Goldberg`s recommended cutoff: no anxiety (0 score) (n = 832), mild anxiety (1–4 score) (n = 403), and moderate/severe anxiety

(5–9 score) (n = 190). We labeled the scores range 5–9 as “moderate/severe” to capture possible variation in anxiety disturbance above a score of five.

To study the changes of anxiety symptoms over time, we constructed a secondary sample from the main analytic sample (Figure 1). In this sample, we classified participants according to GAS scores at baseline and at follow-up into the following four groups: never anxious (0 score at baseline and 0 score at follow-up) (n = 410), incident anxiety (0 score at baseline and ≥5 score at follow-up) (n = 102), persistent anxiety (≥5 score at baseline and ≥5 score at follow-up) (n = 100), and receded anxiety (≥5 score at baseline and 0 score at follow-up) (n = 29). For these analyses, we excluded participants (n = 784) with mild anxiety symptoms at both baseline and at follow-up in order to capture the largest changes in anxiety (from/to moderate/severe anxiety and no anxiety).

It should be noted that there are no reliability or validity information for the GAS in the oldest old, and few studies examined the psychometric evidence for GAS use in older adults (Cronbach’s alpha = 0.82, kappa = −0.13–0.28) (Therrien & Hunsley, 2012).

Measurement of clinical cognitive status

At the follow-up visit, an expanded neuropsychological test battery was administered to participants by centrally trained clinic staff. Tests included the Modified Mini-Mental State Examination (3MS, 100-point) (Teng & Chui, 1987), the Trailmaking Test B (Trails B) (Reitan & Wolfson, 1985), the California Verbal Learning Test, Second Edition (CVLT-II) with immediate and 10-minute delay scores (Delis, Kramer, Kaplan, & Ober, 2000), the Digit Span with forward and backward scores (Wechsler, 1997), and verbal fluency tests (Spreen & Strauss, 1991). The 3MS included items covering orientation, concentration, language, praxis, and memory. In the Trails B test, participants connected a series of alternating numbers and letters. In the Digit Span test, participants were presented with a list of numbers and then were asked to repeat the list in the correct order in forward and backward manners. These tests assessed multiple cognitive domains, including global cognition (3MS), executive function and information processing speed (Trails B), verbal learning and memory (CVLT-II), attention (forward Digit Span), working memory (backwards Digit Span), phonemic fluency (number of words beginning with “f” named in one minute), and category fluency (number of vegetables named in one minute).

A diagnosis of dementia or MCI was established for participants using a two-stage process. First, participants were screened for cognitive impairment. To screen positive for cognitive impairment, participants needed to meet one or more of the following five criteria: a score <88 on the 3MS; a score <4 on the CVLT-II delayed recall; a score ≥3.6 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm & Jacomb, 1989); a self-report of dementia diagnosis; or a nursing home residence. Second, a panel of clinical experts adjudicated the status of those who had screened positive according to one or more of the above criteria, while those who had not met any of the above criteria were considered as having normal cognition. One member of the clinical experts panel was randomly selected to adjudicate the cognitive status for each participant. The information used for adjudication included the following: test scores from the neuropsychological test battery described earlier, depression score, functional status, medications, prior cognitive test scores,

and medical history. The panel of clinical experts included geropsychologist, a neurologist, and two neuropsychologists, and had substantial agreement as demonstrated by an average weighted kappa of 0.77 for inter-rater reliability of diagnoses. Diagnoses of dementia syndromes and MCI were made according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (American Psychiatric Association, 2000) and modified Petersen criteria (Petersen et al., 2001), respectively. More information about the above clinical adjudication process has been published elsewhere (Yaffe et al., 2011). It is noteworthy that the clinical adjudication was completed before DSM-5 was published, but in current terminology dementia would be subsumed under Major Neurocognitive Disorder and MCI would be called Mild Neurocognitive Disorder (American Psychiatric Association, 2013).

Measurement of cognitive decline

To measure cognitive decline between the baseline and the follow-up visits, we used data on a slightly shorter version of the MMSE (short-MMSE, 26-point) that was available for both visits — the full version of the MMSE (30-point) was not administered at the follow-up visit. The short-MMSE did not include questions regarding language and was previously used in other studies (Yaffe et al., 2011; Zeki Al Hazzouri et al., 2014). Lower scores in short-MMSE indicate poorer cognitive function. We defined clinically significant cognitive decline as a change in short-MMSE score of at least one standard deviation from mean change between baseline and follow-up. This difference was equivalent to a loss of 3.33 or more points over time on the short-MMSE. The reference group included participants who maintained their scores, those with improved scores, and those who declined less than one standard deviation.

Measurement of demographic and health-related factors

At the baseline visit, data about demographic and health-related factors were collected via self-report questionnaires (Cummings et al., 1995). Demographic information included age, education, race, and marital status. Medical history was defined as a self-reported prior physician diagnosis of select medical conditions including stroke, myocardial infarction, congestive heart failure, hypertension, chronic obstructive pulmonary disease, diabetes, osteoarthritis, rheumatoid arthritis, and breast cancer. 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 gathering information about difficulty carrying out six instrumental activities of daily living (IADL), which included preparing meals, climbing up to 10 steps, walking down 10 steps, walking two to three blocks on level ground, 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) (Sheikh & Yesavage, 1986) was used to assess depressive symptoms and the standard cutoff score of six or more was used to define depression. The Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was used to assess sleep and the standard cutoff score of five or more was used to define poor sleep. Participants were asked to bring all prescription and non-prescription medications they used in the past month to their clinic visit appointments in order to obtain data on medication use. An interviewer collected the medication information during home visits. Current medication

use (past month) was verified by inspecting medication bottle labels. Medications were coded and categorized using the Iowa Drug Information Service scheme (Pahor et al., 1994).

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. Prior to those comparisons, we examined normality of the data to determine the appropriate tests. Next, a series of unadjusted and multivariable-adjusted logistic regression models of the relationship between anxiety symptoms, and dementia, MCI and cognitive decline were fit. Based on literature from the same study population (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. Model diagnostics were performed including calculation of the Pregibon delta-beta influence statistic, a measure of the relative influence of observations on logistic regression model coefficients. All statistical analyses were conducted with Stata version 13.1 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of participants

Baseline characteristics of participants are presented in Tables 1 and 2. At baseline, 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 with those with no anxiety symptoms. After mean follow-up duration 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 at baseline 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 with those who maintained normal cognition.

Anxiety symptoms and clinical cognitive status

The models of clinical cognitive status by anxiety symptoms are presented in Tables 3 and 4. Women with mild anxiety symptoms at baseline were 1.58 times more likely to develop dementia at follow-up compared with those with no anxiety symptoms at baseline (unadjusted odds ratio (OR) = 1.58, 95% confidence interval [CI] 1.14–2.18, p = 0.005). This association remained statistically significant after adjusting for potential confounders with a multivariable-adjusted OR of 1.66 (95% CI 1.12–2.45, p = 0.012). Moderate/severe anxiety symptoms, however, were not significantly associated with risk of dementia

(multivariable-adjusted OR = 1.27, 95% CI 0.71–2.28, p = 0.425). Overall, the three-level categorical variable for anxiety in this multivariable-adjusted model remained a significant predictor of dementia (Wald (2) = 6.34, p = 0.042). The significant association between any symptom of anxiety and dementia (multivariable-adjusted OR = 1.56, 95% CI 1.07–2.26), p = 0.020) is likely to be driven by mild anxiety, as demonstrated by the significant association of only mild anxiety with dementia in the model with three-level categorical variable. There were no significant associations between any level of anxiety symptoms and risk of MCI in any model.

Women who had moderate/severe anxiety symptoms at baseline and no anxiety symptoms at follow-up (receded anxiety) were 2.81 times more likely to have dementia at follow-up compared with those who were never anxious (unadjusted OR = 2.81, 95% CI 1.17–6.74, p = 0.021). The association between receded anxiety and dementia remained significant after adjusting for potential confounders (multivariable-adjusted OR = 3.80, 95% CI 1.22–11.87, p = 0.021). Similarly, women with no anxiety symptoms at baseline and developed moderate/severe anxiety symptoms at follow-up (incident anxiety) were 1.85 times more likely to have dementia at follow-up compared with those who were never anxious (unadjusted OR = 1.85, 95% CI 1.01–3.39, p = 0.045). However, the association between incident anxiety and dementia did not remain significant after adjusting for potential confounders (multivariable-adjusted OR = 1.54, 95% CI 0.74, 3.20, p = 0.247). Persistent anxiety symptoms over time were not significantly associated with dementia. There were no significant associations between any change of anxiety symptoms over time and risk of MCI in the multivariable-adjusted model.

Anxiety symptoms and clinically significant cognitive decline

In total, 256 (19%) women had clinically significant cognitive decline in short-MMSE over time. Compared with women who had no anxiety symptoms at baseline, women with mild anxiety symptoms were more likely to have cognitive decline (unadjusted OR = 1.40, 95% CI 1.04, 1.90, p = 0.029). However, this association did not remain significant after adjusting for potential confounders (multivariable-adjusted OR = 1.24, 95% CI 0.87, 1.76, p = 0.233). Moderate/severe anxiety symptoms or any change in anxiety symptoms over time were not significantly associated with cognitive decline (data not shown).

Discussion

This prospective cohort 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. In the unadjusted model, change in anxiety symptoms over time, as denoted by both incident and receded anxiety symptoms, was associated with dementia at follow-up. To our knowledge, this is the first study to assess the relationship between levels of and changes in anxiety symptoms and subsequent development of dementia and MCI in the oldest old community-dwelling women.

Our finding of significant association between any or mild anxiety symptoms and dementia is consistent with previous work that showed an overall significant association between anxiety symptoms or disorders, and subsequent cognitive impairment (Burton et al., 2013;

Gallacher et al., 2009; Geda et al., 2014; Pietrzak et al., 2012; Potvin et al., 2011; Sinoff & Werner, 2003). Notwithstanding the methodological differences in these studies that we stated earlier, our work extends their overall finding to the oldest old women. We are aware of very few studies that examined multiple levels of anxiety in relation to cognitive impairment. For instance, a study by Potvin et al. (2011) classified participants into four groups of anxiety symptoms as follows: 1) symptoms meeting DSM-IV criteria for an anxiety disorder; 2) clinically significant anxiety symptoms; 3) not clinically significant anxiety symptoms, and 4) absent anxiety symptoms. That study found significant association between "not clinically significant anxiety symptoms" and general cognitive impairment (MMSE <15th percentile) in older women after one-year follow-up. Our study replicated this finding in the oldest old women after five-year follow-up and using clinically adjudicated cognitive outcome. A study by Okereke and Grodstein (2013) classified participants into five groups of phobic anxiety but included women with a mean age of 63 years, and as such, is not comparable to our study. We are not aware of prior studies that examined course of anxiety symptoms over time in relation to cognitive impairment. A study by Bierman et al. (2008) investigated anxiety scores at four time points in relation to cognitive function tests rather than to a categorical outcome of cognitive impairment, and as such, is not comparable to our study. Therefore, our finding of association between changes, and not persistence, of anxiety symptoms over time and dementia needs to be explored in future studies. Finally, it is important to note that other studies did not find significant association between anxiety symptoms or disorders, and subsequent cognitive impairment (Bierman et al., 2008; Cherbuin et al., 2009; de Bruijn et al., 2014).

The current framework for investigating neuropsychiatric symptoms in relation to late-life cognitive impairment has been dominated by two major themes. One theme considers those neuropsychiatric symptoms as manifestations of the same neurodegenerative disease as the cognitive disorder, while the other theme considers some of these neuropsychiatric symptoms as reflecting separate disorders that could potentially elevate risk of the cognitive disorder. The contradictory findings of the studies investigating this issue may be explained by methodological differences in samples and measurements. Further, two other methodological aspects are particularly instrumental in these studies: length of follow-up and number of assessed neuropsychiatric symptoms. A longer length of follow-up and an accounting for other co-morbid neuropsychiatric symptoms can immensely improve our understanding of the nature of the relationship between neuropsychiatric symptoms and late-life cognitive impairment.

In an attempt to explain the relationship between anxiety symptoms or disorders, and cognitive impairment, three hypotheses have been advanced in the literature. 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 only mild anxiety symptoms were associated with only severe cognitive impairment, and as such, we conclude that our study does not support this hypothesis. This conclusion is based on an assumption that levels of anxiety symptoms and levels of cognitive impairment reflect similar continuum of pathological processes across each level, which cannot be confirmed or ruled out by the measurements in our study. Persistent anxiety symptoms over time were not

associated with risk of cognitive impairment, yielding support to our conclusion regarding this hypothesis.

Second, association between anxiety and cognitive impairment could be confounded by shared risk factors, such as depression. However, we adjusted in our study for a large number of potential confounders, and as such, this hypothesis is less likely to explain our findings.

Third, anxiety could be a consequence of cognitive impairment. Dementia is a neurodegenerative 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 a formal diagnosis of a significant cognitive impairment is made. Our findings could be explained by this hypothesis if we consider mild anxiety symptoms as “prodromal symptoms” of undiagnosed cognitive impairment, and moderate/severe anxiety symptoms as “true symptoms” of an anxiety disorder: only mild anxiety was a significant predictor of dementia. This hypothesis 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 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 dementia may reflect clinical and pathological heterogeneity in our sample. While some persons with early cognitive impairment may have poor judgment and loss of perception, which may hinder their ability to report anxiety symptoms, others may not have similar presentation (American Psychiatric Association, 2013). Loss of insight, inability to properly perceive changes in own personality and behavior, was found to be consistent among patients with frontotemporal dementia and Alzheimer’s disease (Hornberger et al., 2014). In addition, it is known that some persons with MCI may remain stable, some may progress to dementia, and others may return to normal cognition (Palmer et al., 2007). This greater clinical and pathological heterogeneity in MCI, compared with dementia, may explain our finding of no significant association between anxiety and MCI, despite finding an association with dementia.

Strengths of this study include 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. This study has several limitations. First, our study sample was comprised of mostly Caucasian oldest old women, which hinders generalizability of findings to younger women, other ethnic groups, and men. Our study also did not include participants from all SOF study sites. Second, anxiety symptoms were self-reported and were not assessed clinically. We used an instrument that was not developed for use in older adults, however, GAS measures common symptoms of anxiety and has shown moderate validity in a sample of older adults (Pachana et al., 2007). Third, we did not exclude participants with probable cognitive impairment at baseline based on clinical measures, and as such, our sample may have included participants with subtle cognitive impairment. However, we used established criteria to exclude participants who showed signs of cognitive impairment. Fourth, lack of statistical power

may explain the reported lack of association between moderate/severe anxiety and cognitive impairment. Finally, we could not adjust for residual confounding inherent in the observational design of the study.

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

Acknowledgments

The Study of Osteoporotic Fractures (SOF) is supported by National Institutes of Health funding. The National Institute on Aging (NIA) provides support under the following grant numbers: R01 AG005407, R01 AR35582, R01 AR35583, R01 AR35584, R01 AG005394, R01 AG027574, and R01 AG027576. Dr. Mary Ganguli is supported by grant number K07AG044395.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed., text rev). Washington, DC: 2000.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5. 2013.

Andreescu C, Teverovsky E, Fu B, Hughes TF, Chang CC, Ganguli M. Old worries and new anxieties: behavioral symptoms and mild cognitive impairment in a population study. Am J Geriatr Psychiatry. 2014; 22(3):274–284. DOI: 10.1016/j.jagp.2012.09.010 [PubMed: 23759435]

Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. The global burden of anxiety disorders in 2010. Psychol Med. 2014; :1–12. DOI: 10.1017/S0033291713003243

Beaudreau SA, O'Hara R. Late-life anxiety and cognitive impairment: a review. Am J Geriatr Psychiatry. 2008; 16(10):790–803. DOI: 10.1097/JGP.0b013e31817945c3 [PubMed: 18827225]

Beaudreau SA, O'Hara R. The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. Psychol Aging. 2009; 24(2):507–512. DOI: 10.1037/a0016035 [PubMed: 19485667]

Bierman EJ, Comijs HC, Jonker C, Beekman AT. Effects of anxiety versus depression on cognition in later life. Am J Geriatr Psychiatry. 2005; 13(8):686–693. DOI: 10.1176/appi.ajgp.13.8.686 [PubMed: 16085784]

Bierman EJ, Comijs HC, Rijmen F, Jonker C, Beekman AT. Anxiety symptoms and cognitive performance in later life: results from the longitudinal aging study Amsterdam. Aging Ment Health. 2008; 12(4):517–523. DOI: 10.1080/13607860802224276 [PubMed: 18791901]

Billioti de Gage S, Begaud B, Bazin F, Verdoux H, Dartigues JF, Peres K, Pariente A. Benzodiazepine use and risk of dementia: prospective population based study. BMJ. 2012; 345:e6231.doi: 10.1136/bmj.e6231 [PubMed: 23045258]

Burton C, Campbell P, Jordan K, Strauss V, Mallen C. The association of anxiety and depression with future dementia diagnosis: a case-control study in primary care. Fam Pract. 2013; 30(1):25–30. DOI: 10.1093/fampra/cms044 [PubMed: 22915794]

Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2):193–213. [PubMed: 2748771]

Byers AL, Yaffe K. Depression and risk of developing dementia. Nat Rev Neurol. 2011; 7(6):323–331. DOI: 10.1038/nrneurol.2011.60 [PubMed: 21537355]

Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML. High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. Arch Gen Psychiatry. 2010; 67(5):489–496. DOI: 10.1001/archgenpsychiatry.2010.35 [PubMed: 20439830]

Cherbuin N, Reglade-Meslin C, Kumar R, Jacomb P, Easteal S, Christensen H, Anstey KJ. Risk factors of transition from normal cognition to mild cognitive disorder: the PATH through Life Study. Dement Geriatr Cogn Disord. 2009; 28(1):47–55. DOI: 10.1159/000229025 [PubMed: 19628940]

Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Vogt TM. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995; 332(12):767–773. DOI: 10.1056/NEJM199503233321202 [PubMed: 7862179]

de Beurs E, Beekman A, Geerlings S, Deeg D, Van Dyck R, Van Tilburg W. On becoming depressed or anxious in late life: similar vulnerability factors but different effects of stressful life events. Br J Psychiatry. 2001; 179:426–431. [PubMed: 11689400]

de Bruijn RF, Direk N, Mirza SS, Hofman A, Koudstaal PJ, Tiemeier H, Ikram MA. Anxiety Is Not Associated with the Risk of Dementia or Cognitive Decline: The Rotterdam Study. Am J Geriatr Psychiatry. 2014; doi: 10.1016/j.jagp.2014.03.001

Delis, D., Kramer, J., Kaplan, E., Ober, B. California Verbal Learning Test - Second Edition (CVLT-II). San Antonio, TX: Psychological Corporation; 2000.

Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–198. [PubMed: 1202204]

Gallacher J, Bayer A, Fish M, Pickering J, Pedro S, Dunstan F, Ben-Shlomo Y. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. Psychosom Med. 2009; 71(6):659–666. DOI: 10.1097/PSY.0b013e3181a6177c [PubMed: 19553290]

Gallacher J, Elwood P, Pickering J, Bayer A, Fish M, Ben-Shlomo Y. Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS). J Epidemiol Community Health. 2012; 66(10):869–873. DOI: 10.1136/jech-2011-200314 [PubMed: 22034632]

Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D, Lawlor BA. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. Int J Geriatr Psychiatry. 2011; 26(2):166–172. DOI: 10.1002/gps.2509 [PubMed: 21229599]

Ganguli M. Depression, cognitive impairment and dementia: Why should clinicians care about the web of causation? Indian J Psychiatry. 2009; 51(Suppl 1):S29–34. [PubMed: 21416013]

Geda YE, Roberts RO, Knopman DS, Petersen RC, Christianson TJ, Pankratz VS, Rocca WA. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. Arch Gen Psychiatry. 2008; 65(10):1193–1198. DOI: 10.1001/archpsyc.65.10.1193 [PubMed: 18838636]

Geda YE, Roberts RO, Mielke MM, Knopman DS, Christianson TJ, Pankratz VS, Rocca WA. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. Am J Psychiatry. 2014; 171(5):572–581. DOI: 10.1176/appi.ajp.2014.13060821 [PubMed: 24700290]

Goldberg D, Bridges K, Duncan-Jones P, Grayson D. Detecting anxiety and depression in general medical settings. BMJ. 1988; 297(6653):897–899. [PubMed: 3140969]

Gum AM, King-Kallimanis B, Kohn R. Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. Am J Geriatr Psychiatry. 2009; 17(9):769–781. DOI: 10.1097/JGP.0b013e3181ad4f5a [PubMed: 19700949]

Hornberger M, Yew B, Gilardoni S, Mioshi E, Gleichgerrcht E, Manes F, Hodges JR. Ventromedial-frontopolar prefrontal cortex atrophy correlates with insight loss in frontotemporal dementia and Alzheimer's disease. Hum Brain Mapp. 2014; 35(2):616–626. DOI: 10.1002/hbm.22200 [PubMed: 23125121]

Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med. 1989; 19(4):1015–1022. [PubMed: 2594878]

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR. National Comorbidity Survey, R. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289(23):3095–3105. DOI: 10.1001/jama.289.23.3095 [PubMed: 12813115]

Lagnaoui R, Begaud B, Moore N, Chaslerie A, Fourrier A, Letenneur L, Moride Y. Benzodiazepine use and risk of dementia: a nested case-control study. J Clin Epidemiol. 2002; 55(3):314–318. [PubMed: 11864804]

Lopez OL, Becker JT, Sweet RA, Klunk W, Kaufer DI, Saxton J, DeKosky ST. Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 2003; 15(3):346–353. [PubMed: 12928511]

Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA. 2002; 288(12):1475–1483. [PubMed: 12243634]

Mantella RC, Butters MA, Dew MA, Mulsant BH, Begley AE, Tracey B, Lenze EJ. Cognitive impairment in late-life generalized anxiety disorder. Am J Geriatr Psychiatry. 2007; 15(8):673–679. DOI: 10.1097/JGP.0b013e31803111f2 [PubMed: 17426260]

Mehta KM, Simonsick EM, Penninx BW, Schulz R, Rubin SM, Satterfield S, Yaffe K. Prevalence and correlates of anxiety symptoms in well-functioning older adults: findings from the health aging and body composition study. J Am Geriatr Soc. 2003; 51(4):499–504. [PubMed: 12657069]

Okereke OI, Grodstein F. Phobic anxiety and cognitive performance over 4 years among community-dwelling older women in the Nurses' Health Study. Am J Geriatr Psychiatry. 2013; 21(11):1125–1134. 10.1097/JGP.0b013e318267018c. DOI: 10.1016/j.jagp.2013.01.050 [PubMed: 23567369]

Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E. Development and validation of the Geriatric Anxiety Inventory. Int Psychogeriatr. 2007; 19(1):103–114. DOI: 10.1017/S1041610206003504 [PubMed: 16805925]

Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol. 1994; 10(4):405–411. [PubMed: 7843344]

Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology. 2007; 68(19):1596–1602. DOI: 10.1212/01.wnl.0000260968.92345.3f [PubMed: 17485646]

Paterniti S, Dufouil C, Alperovitch A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. J Clin Psychopharmacol. 2002; 22(3):285–293. [PubMed: 12006899]

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Winblad B. Current concepts in mild cognitive impairment. Arch Neurol. 2001; 58(12):1985–1992. [PubMed: 11735772]

Pietrzak RH, Maruff P, Woodward M, Fredrickson J, Fredrickson A, Krystal JH, Darby D. Mild worry symptoms predict decline in learning and memory in healthy older adults: a 2-year prospective cohort study. Am J Geriatr Psychiatry. 2012; 20(3):266–275. DOI: 10.1097/JGP.0b013e3182107e24 [PubMed: 22354117]

Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Wallace RB. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007; 29(1–2):125–132. DOI: 10.1159/000109998 [PubMed: 17975326]

Potvin O, Forget H, Grenier S, Preville M, Hudon C. Anxiety, depression, and 1-year incident cognitive impairment in community-dwelling older adults. J Am Geriatr Soc. 2011; 59(8):1421–1428. DOI: 10.1111/j.1532-5415.2011.03521.x [PubMed: 21797836]

Reitan, R., Wolfson, D. The Halstead-Reitan Neuropsychological Battery: Theory and Clinical Interpretation. Tuscon, AZ: Neuropsychology Press; 1985.

Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. 1986; 5:165–173.

Sinoff G, Werner P. Anxiety disorder and accompanying subjective memory loss in the elderly as a predictor of future cognitive decline. Int J Geriatr Psychiatry. 2003; 18(10):951–959. DOI: 10.1002/gps.1004 [PubMed: 14533128]

Spira AP, Stone K, Beaudreau SA, Ancoli-Israel S, Yaffe K. Anxiety Symptoms and Objectively Measured Sleep Quality in Older Women. Am J Geriatr Psychiatry. 2009; 17(2):136–143. DOI: 10.1097/JGP.0b013e3181871345 [PubMed: 19155746]

Spreen, O., Strauss, E. A Compendium of Neuropsychological Tests: Administration, Norms and Commentary. New York, NY: Oxford University Press; 1991.

Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry. 1987; 48(8):314–318. [PubMed: 3611032]

Therrien Z, Hunsley J. Assessment of anxiety in older adults: a systematic review of commonly used measures. Aging Ment Health. 2012; 16(1):1–16. DOI: 10.1080/13607863.2011.602960 [PubMed: 21838650]

United Nations. World Population Ageing 2015. 2015

van Hout HP, Beekman AT, de Beurs E, Comijs H, van Marwijk H, de Haan M, Deeg DJ. Anxiety and the risk of death in older men and women. Br J Psychiatry. 2004; 185:399–404. DOI: 10.1192/bjp.185.5.399 [PubMed: 15516548]

Wechsler, D. Wechsler Adult Intelligence Scale-III. San Antonio, TX: Psychological Corporation; 1997.

Wetherell JL, Reynolds CA, Gatz M, Pedersen NL. Anxiety, cognitive performance, and cognitive decline in normal aging. J Gerontol B Psychol Sci Soc Sci. 2002; 57(3):P246–255. [PubMed: 11983736]

World Health Organization. Dementia a public health priority. 2012. Retrieved December 1, 2016, from http://www.who.int/mental_health/publications/dementia_report_2012/en/index.html

Yaffe K, Boustani M. Benzodiazepines and risk of Alzheimer's disease. BMJ. 2014; 349:g5312.doi: 10.1136/bmj.g5312 [PubMed: 25205606]

Yaffe K, Middleton LE, Lui LY, Spira AP, Stone K, Racine C, Kramer JH. Mild cognitive impairment, dementia, and their subtypes in oldest old women. Arch Neurol. 2011; 68(5):631–636. DOI: 10.1001/archneurol.2011.82 [PubMed: 21555638]

Zeki Al Hazzouri A, Vittinghoff E, Byers A, Covinsky K, Blazer D, Diem S, Yaffe K. Long-term cumulative depressive symptom burden and risk of cognitive decline and dementia among very old women. J Gerontol A Biol Sci Med Sci. 2014; 69(5):595–601. DOI: 10.1093/gerona/glt139 [PubMed: 24097423]

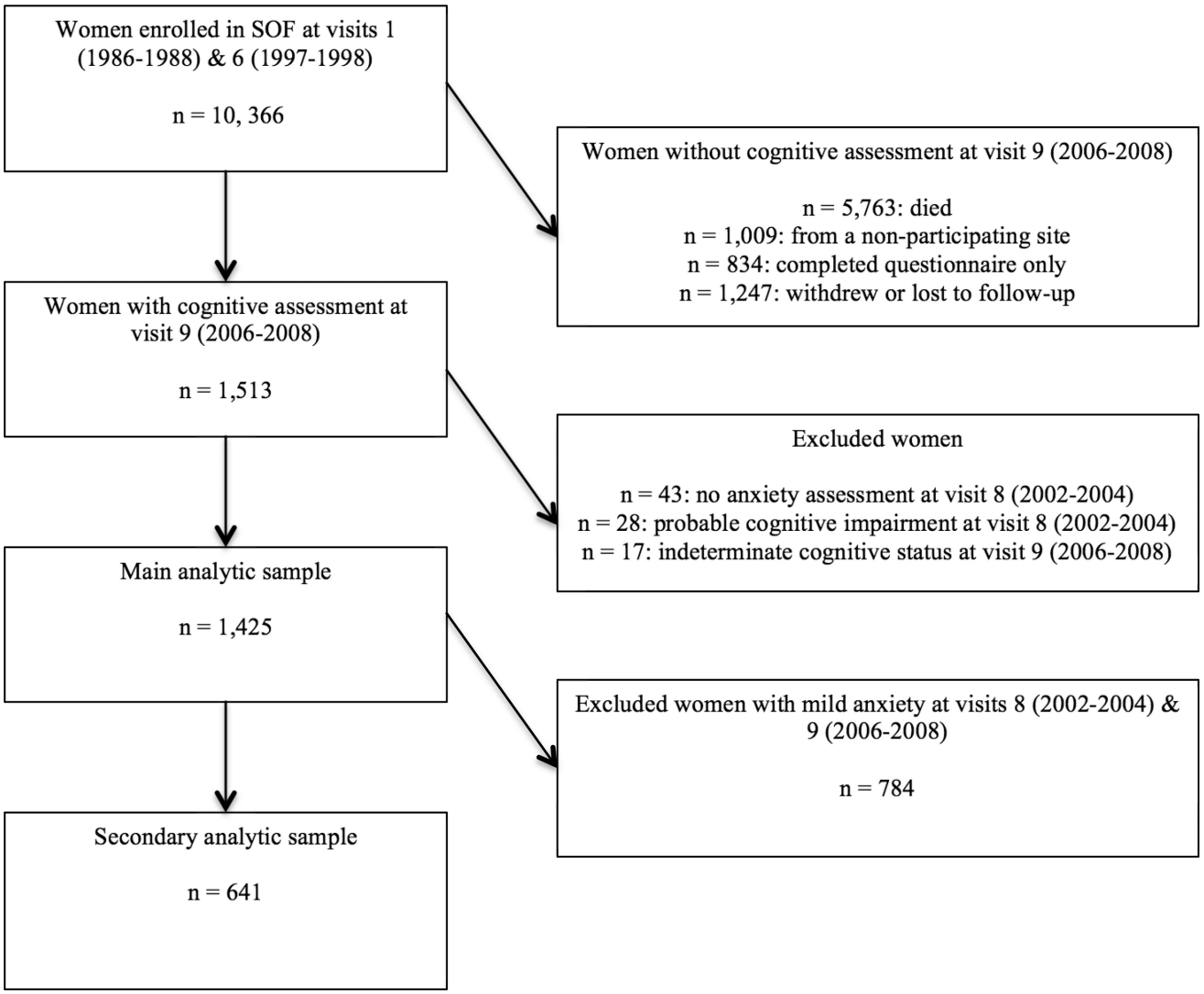

Figure 1.
Sample Flow Chart

Table 1

Baseline characteristics of participants according to level of anxiety symptoms at baseline in the oldest old women

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

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	
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
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

*Based on 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

Aging Ment Health. Author manuscript; available in PMC 2019 April 01.

Table 2

Baseline characteristics of participants according to clinical cognitive status at follow-up in the oldest old women

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)	18 (7.7)	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

Characteristics	Total N = 1,425	Cognitive status			p-value*
		Normal cognition N = 857	Mild cognitive impairment N = 335	Dementia N = 233	
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

*Based on 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

Table 3

Association between anxiety symptoms and dementia in the oldest old women

Logistic regression	Anxiety symptoms	Unadjusted		Multivariable-adjusted*	
		Odds ratio (95% confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Model 1	Any	†1.47 (1.10–1.97)	0.009	†1.56 (1.07–2.26)	0.020
	None	1.00 (reference)			
Model 2	Moderate/ severe	1.27 (0.82–1.96)	0.289	1.27 (0.71–2.28)	0.425
	Mild	†1.58 (1.14–2.18)	0.005	†1.66 (1.12–2.45)	0.012
	None	1.00 (reference)			
Model 3	Incident	†1.85 (1.01–3.39)	0.045	1.54 (0.74–3.20)	0.247
	Persistent	1.08 (0.58–2.03)	0.809	0.83 (0.34–2.03)	0.690
	Receded	†2.81 (1.17–6.74)	0.021	†3.80 (1.22–11.87)	0.021
	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

†p<0.05

Table 4

Association between anxiety symptoms and mild cognitive impairment in the oldest old women

Logistic regression	Anxiety symptoms	Unadjusted		Multivariable-adjusted*	
		Odds ratio (95% confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Model 1	Any	1.05 (0.81–1.35)	0.726	1.07 (0.78–1.47)	0.663
	None	1.00 (reference)			
Model 2	Moderate/ severe	0.98 (0.67–1.45)	0.931	0.99 (0.60–1.62)	0.969
	Mild	1.08 (0.81–1.44)	0.608	1.10 (0.79–1.55)	0.574
	None	1.00 (reference)			
Model 3	Incident	†2.26 (1.37–3.73)	0.001	1.73 (0.95–3.15)	0.071
	Persistent	0.96 (0.55–1.67)	0.872	0.80 (0.38–1.70)	0.564
	Receded	1.03 (0.37–2.93)	0.949	1.10 (0.31–3.84)	0.885
	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

†p<0.05