Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Int Psychogeriatr. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Int Psychogeriatr. 2017 July ; 29(7): 1137–1145. doi:10.1017/S104161021700045X.

Anxiety Symptoms and Risk of Cognitive Decline in Older Community-Dwelling Men

Ahmed M. Kassem[1], **Mary Ganguli**[1,2], **Kristine Yaffe**[3], **Joseph T. Hanlon**[1,4], **Oscar L. Lopez**[2], **John W. Wilson**[5], and **Jane A. Cauley**[1] **for the Osteoporotic Fractures in Men (MrOS) Study Research Group**

[1]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA 15261, USA

[2]Departments of Psychiatry and Neurology, University of Pittsburgh, Pittsburgh, PA 15261, USA

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

[4]Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15261, USA

[5]Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA 15261, USA

Abstract

Background—Previous research regarding anxiety as a predictor of future cognitive decline in older adults is limited and inconsistent. 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).

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 substantial 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).

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.

Conflict of interest

None

Description of authors' roles

JAC is the principal investigator of the MrOS study. AMK and JAC formulated the research questions and designed the study. AMK analyzed the data and drafted the manuscript. All co-authors interpreted the results and contributed to the preparation of the final manuscript and approved the manuscript. In addition, the MrOS Publications Committee approved the study.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Conclusion—In cognitively healthy older men, mild anxiety symptoms may potentially predict future decline in executive functioning. Anxiety is likely a manifestation of an underlying neurodegenerative process rather than a cause.

Keywords

anxiety; cognitive decline; executive function; older men

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 (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 (Mantella *et al.*, 2007; Yochim *et al.*, 2013), and elevated anxiety symptoms in older adults with cognitive impairment (Andreescu *et al.*, 2014; Lopez *et al.*, 2003). Second, longitudinal studies have suggested that anxiety increased the risk of progression of mild cognitive impairment (MCI) to dementia (Gallagher *et al.*, 2011). Third, a number of studies reported that the use of benzodiazepines, a group of anxiolytic medications, was associated with risk of dementia or cognitive decline (Billioti de Gage *et al.*, 2012; 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 and Boustani, 2014). Finally, there is a high co-occurrence between anxiety and depression (Byers *et al.*, 2010), which itself is a potential risk factor for cognitive impairment (Byers and Yaffe, 2011; Ganguli, 2009).

The longitudinal relationship between anxiety and subsequent cognitive impairment in older adults remains unclear (Beaudreau and 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; Pietrzak *et al.*, 2012; Potvin *et al.*, 2011; Sinoff and 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 influences on men and women. Compared with women, men with anxiety had lower disability (Baxter *et al.*, 2014) but higher mortality (van Hout *et al.*, 2004). Differences in biological, behavioral or social factors that contribute to distinctive pathophysiological features in men and women may explain these findings. Therefore, it is appropriate to investigate anxiety separately among

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

men and women. We are aware of only one prospective study that examined the association of anxiety with dementia and "cognitive impairment not dementia" 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.

Methods

Population

We utilized data from MrOS Study, a prospective cohort study of community-dwelling men aged 65 years and older (Orwoll *et al.*, 2005) (Blank *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 and 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.

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 important disturbance" of anxiety, while higher scores substantially increase the probability of a significant anxiety disorder. 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).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 and 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. Development of substantial cognitive impairment in 3MS was defined as a decline of five points or more between baseline and visit 3 (Andrew and 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. Development of substantial cognitive impairment 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).

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 *et al.*, 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) (Sheikh and Yesavage, 1986) was used to assess depressive symptoms, with the standard cutoff score of 6 or more to define depression. 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).

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 substantial cognitive impairment 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 index (stroke, Parkinson`s disease, myocardial infarction, hypertension, chronic obstructive pulmonary disease, diabetes, and osteoarthritis), 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 $p<0.05$. In all models, we used the 2-level (any anxiety, no anxiety) and 3-level (moderate/severe anxiety, mild anxiety, no anxiety) anxiety variables we defined earlier. 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 Table 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 substantial impairment in global cognitive function and 240 (10%) men had substantial impairment 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.

Anxiety symptoms and 3MS test

The mean baseline and 3-year change in 3MS score by baseline anxiety symptoms is shown in Table 2. In the multivariable-adjusted model, men with no anxiety symptoms at baseline had a mean score of 93.79 points versus 93.56 and 92.78 for those with mild and moderate/severe symptoms, respectively. The decline in 3MS score from baseline to year 3 was larger among men with mild anxiety symptoms compared with those with no symptoms or with moderate/severe symptoms (−1.45 points versus −1.06 and −0.80, respectively). The 3MS scores across anxiety groups were significantly different at baseline ($p=0.003$) and throughout follow-up ($p=0.004$). In all models, there was no significant interaction between

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

anxiety symptoms and time, indicating that anxiety groups did not change differently over time in their global cognition.

The association of anxiety symptoms with substantial impairment in the global cognitive outcome is shown in Table 4. Overall, there was no significant association between anxiety symptoms, including mild and more severe symptoms, and incident substantial cognitive impairment in 3MS at visit 3.

Anxiety symptoms and Trails B test

The mean baseline and 3-year change in Trails B completion time by baseline anxiety symptoms is shown in Table 3. In the multivariable-adjusted model, men with no anxiety symptoms at baseline had a mean test completion time of 115.32 seconds versus 118.04 and 115.73 seconds for those with mild and moderate/severe symptoms, respectively. The decline in Trails B test (increase in completion time) from baseline to year 3 was larger in men with moderate/severe anxiety symptoms compared to those with no symptoms or with mild symptoms (+15.41 seconds versus +8.07 and +11.50, respectively). The Trails B completion times across anxiety groups were not significantly different at baseline (p=0.417) or throughout follow-up (p=0.053). In all models, there was significant interaction between anxiety symptoms and time, indicating that anxiety groups changed differently over time in their executive function. For instance, the significant interaction term (p= 0.036) in the multivariable-adjusted model 2 depicted a faster decline in executive function among men with moderate/severe anxiety (graph not shown).

There was a consistent association between anxiety symptoms and substantial worsening of Trails B test completion time (Table 4). In the multivariable-adjusted model, older men with any anxiety symptoms at baseline were 1.40 times more likely to have incident substantial worsening in Trails B test completion time at visit 3 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, only mild anxiety symptoms remained significant in the multivariable-adjusted model.

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 substantial impairment 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 generally consistent with prospective studies that reported significant associations between anxiety and cognitive impairment, but extend these findings to show that 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 (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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 "general cognitive impairment" (Potvin *et al.*, 2011), 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 (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 within 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. It is often recommended that the score on Trails A be subtracted from the score of Trails B to remove the effect of psychomotor speed. However, we were restricted to instruments that were selected by the original investigators of MrOS and Trails A was not administered. Fourth, we excluded participants with probable cognitive impairment at

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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.

In cognitively healthy older men, our findings suggest that mild anxiety symptoms may potentially predict incident 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. Future research may also investigate the relationship between anxiety and decline in specific cognitive domains, such as executive function, in older women.

Acknowledgments

The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128. The National Heart, Lung, and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study “Outcomes of Sleep Disorders in Older Men” under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839. Dr. Mary Ganguli is supported by grant number K07AG044395.

References

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. American Journal of Geriatric Psychiatry. 2014; 22:274–284. [PubMed: 23759435]

Andrew MK, Rockwood K. A five-point change in Modified Mini-Mental State Examination was clinically meaningful in community-dwelling elderly people. Journal of Clinical Epidemiology. 2008; 61:827–831. [PubMed: 18468855]

Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. The global burden of anxiety disorders in 2010. Psychological Medicine. 2014; 44:2363–2374. [PubMed: 24451993]

Beaudreau SA, O’Hara R. Late-life anxiety and cognitive impairment: a review. American Journal of Geriatric Psychiatry. 2008; 16:790–803. [PubMed: 18827225]

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; 12:517–523. [PubMed: 18791901]

Billioti de Gage S, et al. Benzodiazepine use and risk of dementia: prospective population based study. BMJ. 2012; 345:e6231. [PubMed: 23045258]

Blackwell T, et al. Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: the MrOS sleep study. Sleep. 2014; 37:655–663. [PubMed: 24899757]

Blank JB, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemporary Clinical Trials. 2005; 26:557–568. [PubMed: 16085466]

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. Family Practice. 2013; 30:25–30. [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 Research. 1989; 28:193–213. [PubMed: 2748771]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Byers AL, Yaffe K. Depression and risk of developing dementia. Nature Reviews: Neurology. 2011; 7:323–331. [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. Archives of General Psychiatry. 2010; 67:489–496. [PubMed: 20439830]

Cherbuin N, et al. Risk factors of transition from normal cognition to mild cognitive disorder: the PATH through Life Study. Dementia and Geriatric Cognitive Disorders. 2009; 28:47–55. [PubMed: 19628940]

de Bruijn RF, et al. Anxiety is not associated with the risk of dementia or cognitive decline: the Rotterdam Study. American Journal of Geriatric Psychiatry. 2014; 22:1382–1390. [PubMed: 24745561]

Gallacher J, et al. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. Psychosomatic Medicine. 2009; 71:659–666. [PubMed: 19553290]

Gallagher D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. International Journal of Geriatric Psychiatry. 2011; 26:166–172. [PubMed: 21229599]

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

Ganguli M, et al. Sensitivity and specificity for dementia of population-based criteria for cognitive impairment: the MoVIES project. Journal of Gerontology. 1993; 48:M152–161. [PubMed: 8315228]

Goldberg D, Bridges K, Duncan-Jones P, Grayson D. Detecting anxiety and depression in general medical settings. BMJ. 1988; 297:897–899. [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. American Journal of Geriatric Psychiatry. 2009; 17:769–781. [PubMed: 19700949]

Kuller LH, et al. Risk factors for dementia in the cardiovascular health cognition study. Neuroepidemiology. 2003; 22:13–22. [PubMed: 12566949]

Lopez OL, et al. Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. Journal of Neuropsychiatry and Clinical Neurosciences. 2003; 15:346–353. [PubMed: 12928511]

Mantella RC, et al. Cognitive impairment in late-life generalized anxiety disorder. American Journal of Geriatric Psychiatry. 2007; 15:673–679. [PubMed: 17426260]

Orwoll E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study–a large observational study of the determinants of fracture in older men. Contemporary Clinical Trials. 2005; 26:569–585. [PubMed: 16084776]

Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E. Development and validation of the Geriatric Anxiety Inventory. International Psychogeriatrics. 2007; 19:103–114. [PubMed: 16805925]

Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. European Journal of Epidemiology. 1994; 10:405–411. [PubMed: 7843344]

Paterniti S, Dufouil C, Alperovitch A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. Journal of Clinical Psychopharmacology. 2002; 22:285–293. [PubMed: 12006899]

Pietrzak RH, et al. Mild worry symptoms predict decline in learning and memory in healthy older adults: a 2-year prospective cohort study. American Journal of Geriatric Psychiatry. 2012; 20:266–275. [PubMed: 22354117]

Plassman BL, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007; 29:125–132. [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. Journal of the American Geriatrics Society. 2011; 59:1421–1428. [PubMed: 21797836]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Sheikh J, Yesavage J. Geriatric Depression Scale: recent evidence and development of a shorter version. Clinical Gerontologist. 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. International Journal of Geriatric Psychiatry. 2003; 18:951–959. [PubMed: 14533128]

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

van Hout HP, et al. Anxiety and the risk of death in older men and women. British Journal of Psychiatry. 2004; 185:399–404. [PubMed: 15516548]

Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. Journal of Clinical Epidemiology. 1993; 46:153–162. [PubMed: 8437031]

Wolitzky-Taylor KB, Castriotta N, Lenze EJ, Stanley MA, Craske MG. Anxiety disorders in older adults: a comprehensive review. Depression and Anxiety. 2010; 27:190–211. [PubMed: 20099273]

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

Yochim BP, Mueller AE, Segal DL. Late life anxiety is associated with decreased memory and executive functioning in community dwelling older adults. Journal of Anxiety Disorders. 2013; 27:567–575. [PubMed: 23298889]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Int Psychogeriatr. Author manuscript; available in PMC 2018 July 01.

Table 1

Characteristics of older men 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					

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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)	
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
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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Mean baseline and 3-year change in Modified Mini-Mental State examination (3MS) score by baseline anxiety symptoms in older men

	Anxiety symptoms	Unadjusted		Multivariable-adjusted*	
		Baseline score	3-year change	Baseline score	3-year change
Model 1	Any	93.23	−1.31	93.39	−1.29
	None	93.80	−1.08	93.78	−1.06
	p-value	0.001	0.001	0.021	0.018
Model 2	Moderate/severe	92.53	−0.84	92.78	−0.80
	Mild	93.45	−1.46	93.56	−1.45
	None	93.80	−1.08	93.79	−1.06
	p-value	<0.001	<0.001	0.003	0.004

*Models were adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race, education, marital status, and instrumental activities of daily living impairments.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3

Mean baseline and 3-year change in Trails B completion time by baseline anxiety symptoms in older men

	Anxiety symptoms	Unadjusted		Multivariable-adjusted*	
		Baseline completion time	3-year change in completion time	Baseline completion time	3-year change in completion time
Model 1	Any	120.61	+12.81	117.53	+12.45
	None	114.92	+8.27	115.30	+8.07
	p-value	0.005	0.001	0.251	0.018
Model 2	Moderate/severe	124.42	+15.90	115.73	+15.41
	Mild	119.36	+11.80	118.04	+11.50
	None	114.92	+8.27	115.32	+8.07
	p-value	0.008	0.001	0.417	0.053

*Models were adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race, education, marital status and instrumental activities of daily living impairments.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 4

Association between baseline anxiety symptoms and substantial cognitive impairment at visit 3 in older men

	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)	0.82 (0.53, 1.28)	1.86 (1.19, 2.90)	1.35 (0.81, 2.27)
	Mild	1.17 (0.93, 1.47)	1.13 (0.89, 1.44)	1.47 (1.09, 1.99)	1.41 (1.03, 1.93)
	None	1.00 (reference)			

*Models were adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race, education, marital status and instrumental activities of daily living impairments.

**Models were adjusted for clinic site, age, depression, poor sleep, psychotropic medications, race and instrumental activities of daily living impairments.