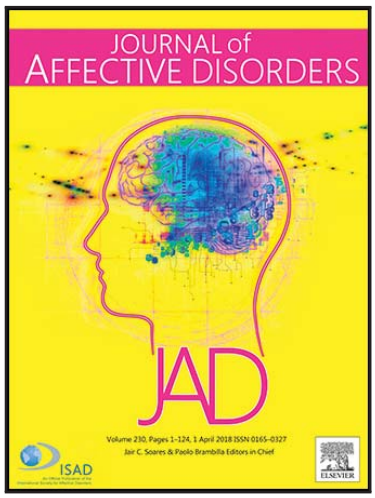
Accepted Manuscript



Clinically relevant anxiety and risk of Alzheimer's disease in an elderly community sample: 4.5 years of follow-up.

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PII: S0165-0327(18)33119-7
DOI: https://doi.org/10.1016/j.jad.2019.02.050
Reference: JAD 10547

To appear in: *Journal of Affective Disorders*

Received date: 11 December 2018
Revised date: 4 February 2019
Accepted date: 17 February 2019

Please cite this article as: J. Santabárbara , B. Villagrasa , R. Lopez-Anton , B. Olaya , J. Bueno-Notivol , C. de la Cámara , P. Gracia-García , E. Lobo , A. Lobo , Clinically relevant anxiety and risk of Alzheimer's disease in an elderly community sample: 4.5 years of follow-up., *Journal of Affective Disorders* (2019), doi: https://doi.org/10.1016/j.jad.2019.02.050

Highlights:

- The risk of Alzheimer's disease was almost 4-fold higher in cases of clinically relevant anxiety compared with non-cases, even when controlling for depression and other potential confounders.
- This finding may stimulate future studies to test the impact of the treatment of anxiety on prevention or delay onset of symptoms of AD.
- The association between subcases of anxiety at baseline and AD risk did not reach statistical significance.

Title: Clinically relevant anxiety and risk of Alzheimer's disease in an elderly community sample: 4.5 years of follow-up.

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KEYWORDS: Anxiety; Alzheimer Disease; risk factor; ZARADEMP; community study.

Word count:

Abstract: 241 words

Text: 2231 words

References: 27

Figures: 0

Tables: 2

Funding / Support: Supported by Grants from the *Fondo de Investigación Sanitaria*, *Instituto de Salud Carlos III*, Spanish Ministry of Economy and Competitiveness, Madrid, Spain (grants 94/1562, 97/1321E, 98/0103, 01/0255, 03/0815, 06/0617, G03/128).

Abstract

Objectives: To investigate whether clinically relevant anxiety increased the risk for developing Alzheimer's disease (AD) while controlling for the presence of depression and other confounders; and to report the population attributable fraction (PAF) associated with anxiety disorder.

Method: We used data from the longitudinal, community-based Zaragoza Dementia and Depression (ZARADEMP) study. A random sample of 4,057 dementia-free community dwellers aged 55 or older were followed for 4.5 years. The Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy package was used for the diagnosis of clinically significant cases and subcases of anxiety; and AD was diagnosed by a panel of research psychiatrists according to DSM-IV criteria. Multivariate survival analysis with competing risk regression model was performed.

Results: We observed a significant association between anxiety cases at baseline and AD risk in the univariate analysis that persisted in the fully adjusted model (SHR: 3.90; 95% CI: 1.59 - 9.60; p=0.003), with a PAF for AD of 6.11% (95% CI: 1.30% - 16.17%). No significant association between 'subcases' of anxiety at baseline and AD was found.

Limitations: Data on apolipoprotein E were not available. The hospital-based diagnosis was not completed in all cases of dementia.

Conclusion: Late life, clinically significant anxiety (but not subclinical anxiety) seems to increase the risk of AD, independently of the effect of several confounders, including depression. Taking into account the high prevalence of anxiety among the elderly, future studies are warranted to determine potential risk reduction of AD.

Introduction

The analysis of risk reduction of dementia and its most frequent type, Alzheimer disease (AD), has been put at stake in a report (Wortmann, 2014) which includes classical modifiable risk factors (lifestyle and cardiovascular factors) but also psychological factors such as depression and anxiety. While the association of depression and AD has been extensively investigated in the last years (Cherbuin et al., 2015), the study of the link between anxiety and AD has only started to be on the spotlight. A recent meta -analysis (Becker et al., 2018) reports that subjects presenting with anxiety have a 53% higher risk for AD, thus postulating anxiety as a potential risk factor for AD. However, the majority of measures used to identify cases of anxiety in the articles included in this meta–analysis have been considered to lack sufficient evidence to warrant their use with older individuals (Therrien & Hunsley, 2012). Since we have shown that clinically relevant anxiety increases the risk of overall dementia (Santabárbara et al., 2018), we now hypothesize that it also is associated with increased AD risk. A second objective was to report the population-attributable fraction (PAF) of AD due to anxiety disorder.

Method

Sample and Procedure

We used data from the Zaragoza Dementia and Depression (ZARADEMP) project, a longitudinal, population-based study intended to document the incidence and risk factors of somatic and psychiatric diseases in adults aged ≥55 years (Lobo et al., 2005). The sample was drawn from Spanish official census lists, included institutionalized individuals and was stratified with proportional allocation by age and sex. Refusal rate was 20.5%, and 4,803 individuals finally participated at baseline (starting in 1994). A two-phase, screening procedure was implemented in the baseline (Wave I) and in the two follow-up waves (Waves II and III) completed for this study. Validated, Spanish versions of international instruments were used for the assessment: the Mini-Mental Status Examination (MMSE); the Geriatric Mental State B (GMS-B); the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) (Copeland et al., 1986); the History and Aetiology Schedule (HAS) (medical and psychiatric history data); the Katz's Index for basic activities of daily living

(bADL's) and the Lawton and Brody scale for instrumental activities (iADL's); and the European Studies of Dementia (EURODEM) Risk Factors Questionnaire (for medical conditions). A more detailed account of the methods has been reported previously (Lobo et al., 2011; Santabarbara et al, 2018).

The Ethics Committee of the University of Zaragoza and the Fondo de Investigación Sanitaria (FIS) approved the study, according to Spanish Law, and principles of written informed consent, privacy, and confidentiality have been maintained throughout the Project.

Alzheimer's Disease assessment and diagnosis

At the end of the baseline assessment, identified cases of dementia and subcases of dementia (GMS –criteria) were excluded for the follow-up waves (II and III). Incident dementia (including subtypes) was initially diagnosed at follow-up by a psychiatrist and the final AD DSM-IV diagnosis was made by consensus that required agreement of at least three psychiatrists in a four- member panel. The validity of this diagnostic process has also been shown (Lobo et al., 1995). To document the accuracy of the panel, some detected cases were invited to a hospital diagnostic work- up, and NINCDS-ADRDA criteria were applied to diagnose AD. Agreement on the diagnosis of dementia and type of dementia was reached in 95.8% and 87.5% of the cases, respectively.

Anxiety Assessment and Diagnosis

Anxiety diagnosis was based on the GMS-AGECAT. This diagnostic approach has been shown to be valid in community samples, and participants with AGECAT confidence levels ≥ 3 in the 0–5 scale are considered to be likely 'cases' of clinically significant anxiety requiring clinical intervention (Copeland et al., 2004). The diagnosis of subsyndromal anxiety ("subcase", confidence levels 1 and 2) implies that the clinical symptoms are not severe enough to require an intervention.

Covariates

The following covariates were used: socio-demographic characteristics (age, sex, educational level, marital status and living alone), medical risk factors (vascular disease, hypertension and diabetes), health status, cognitive status and clinically significant depression. (Santabárbara et al., 2018)

Statistical analysis

We used the Fine and Gray multivariate regression model to calculate the risk of participants for experiencing AD, taking into account the competing event (death) as time progressed and with age as timescale with delayed entry (Thiébaut & Bénichou, 2004).

We estimated the population-attributable fraction (PAF) for AD which might be related to anxiety status and the 95% CI. The PAF tries to estimate the proportion of AD risk that would be avoided if the condition (anxiety) could be prevented, assuming a causal effect and unbiased estimates.

Statistical analyses were conducted using *R* software (*http://www.r-project.org*).

Results

Supplementary Figure 1 illustrates the flow diagram of the ZARADEMP Project. The refusal rate was 20.5%, and 4803 individuals were ultimately interviewed at baseline (ZARADEMP I). Subjects with dementia and subcases of dementia (n=746) were excluded from the two follow-up evaluations (ZARADEMP II and ZARADEMP III). Then, our final sample included 4057 participants without any type of dementia for the 4.5-years follow-up period (median 4.4 years; interquartile range: 3.0- 4.9 years). Baseline characteristics according to anxiety status have been described elsewhere (Santabárbara et al., 2018). In brief, compared with subcases and non-cases, cases of anxiety were more likely to be female, to report bad health status, and to have depression and disabilities for instrumental ADLs.

Table 1 shows initial demographic characteristics according to AD incidence status. The incident AD group was significantly older, more likely to be female, illiterate, widowed, to perform worse cognitively and to have anxiety and functional disabilities. During the 4.5 years follow-up period, 730 (17.9%) individuals died and 849 (20.9%) were lost (Supplementary figure 1). Those lost during follow-up were on average 4.3 years older ($p < 0.001$) and more likely to be illiterate than those re-evaluated; the MMSE scores were also lower among those lost ($p < 0.001$).

The proportion of incident cases of AD increased according to the severity of the anxiety status (Table 2): 1.8% for non-cases, 2.3% for subcases and 6.6% for cases (*p* for trend =

0.038). Table 2 also shows the results of the competing risk regression analysis of AD incidence associated with anxiety status at baseline. The risk of AD was almost 4-fold higher in anxiety cases compared with noncases when all potential confounding factors were controlled (HR: 3.90; 95% CI: 1.59–9.60). No significant association between 'subcases' of anxiety at baseline and AD was found in either model.

We estimated that the proportion of the population with anxiety was 2.24%. This yields a PAF for AD of 6.11% (95% CI: 1.30% -16.17%).

Discussion

Our findings in a sample of community-dwelling adults aged 55+ showed that, compared with subjects without anxiety, the incidence rate of AD during a period of 4.5-years was 3.9 -fold higher among individuals with clinically relevant anxiety, after adjusting for several covariates, including depression. By contrast, this association was not found for subjects with subthreshold anxiety. The PAF documented in this study suggests the possible contribution of anxiety in a considerable proportion of cases (6.1%) to the development of AD in the entire population (Porta, 2008). To our knowledge, this is the first study addressing the effect of clinically relevant anxiety on the risk of AD.

Our results agree with recent meta-analysis indicating a positive and significant association between anxiety and AD in older adults (Becker et al., 2018). However, the magnitude of effect found in our sample was higher, suggesting the importance of using clinical criteria for anxiety. De Bruijn et al (2014) did not find a significant association with AD neither in clinical anxiety (according to DSM criteria) nor in anxiety symptoms in a large community sample of older adults despite controlling for the confounding effect of APOE-4; however, they did not adjust for the competing risk of death which might explain the discrepancies between both studies.

Similar to depression, there is still debate on whether anxiety is a risk factor for AD or it is an early sign of an underlying neurodegenerative process. A recent systematic review (Gimson et al, 2018) reports a positive association between anxiety and risk of dementia over a mean interval of at least 10 years, suggesting that anxiety at midlife is associated with dementia and thus supporting the idea that anxiety is a risk factor rather than a

prodromal state. While our follow-up period was only 4.5 years, our findings also support the notion of increased risk as opposed to prodromal feature, for several reasons. First, to minimize the possibility of including in the cohort individuals with cognitive deficits at baseline, we excluded at baseline all "subcases" of cognitive impairment or dementia (AGECAT criteria) to minimize the possibility of including in the cohort individuals with mild or very mild cognitive deficits.. Second, cognitive status at baseline was controlled in the analysis. Third, it might be argued that individuals with subclinical anxiety were in fact incipient, prodromal cases of AD (Forsell et al., 1993). However, only clinically significant anxiety, but not subclinical anxiety, was associated with AD. If anxiety was prodromic, it would be expected that anxiety subcases would also develop dementia in a 4.5-year period.

Some cojectures may help to explain the increased risk of AD associated with anxiety disorder. Anxiety during lifetime can compromise neuroplasticity and reduce cognitive reserve (Vance et al, 2010). In addition, anxiety could share etiological underlying mechanisms with AD. Some studies (Salim et al., 2012) postulate anxiety as a behavioural consequence of inflammation and oxidative damage to the central nervous system (CNS). Similarly, there is growing evidence for the role of CNS inflammation in the continuum of the AD pathology (Cuello et al., 2017), which starts at very early stages, most likely before amyloid plaques are formed. Moreover, recent studies suggest a bi-directional association between amyloid-β (Aβ) and anxiety. High anxiety levels in Aβ+ individuals have been found to be associated with faster cognitive decline (Pietrzak et al, 2015), and higher amyloid beta burden to be associated with increasing anxious-depressive symptoms over time in cognitively normal older individuals (Donovan et al, 2018).

Our results also suggest that the association between anxiety in older adults and AD is independent from several confounders, including education, cognitive status, medical conditions and particularly depression. Depression has been consistently associated with increased risk for AD (Gracia-García et al, 2013). Thus, our findings would support the idea that anxiety is acting on the brain through pathways different than depression. This warrants future research.

Our study had several strengths, including a representative population sample, containing institutionalized individuals, a longitudinal design, the use of high sensitivity and specificity of case finding with validated instruments, the use of age as timescale, and the inclusion of actual mortality data in the Fine and Gray model to study anxiety as a risk factor for AD. Furthermore, this was the first investigation using a competing risk model to study anxiety as a risk factor for AD, which estimates risk more accurately than traditional models (e.g., Kaplan-Meier and Cox regression) (Berry et al., 2010).

Limitations

Among the limitations, we should mention the small number of subjects with clinically significant anxiety that developed AD, the absence of data on apolipoprotein E, and the fact that the hospital-based diagnosis was not completed in all cases of dementia. Furthermore, we did not control for family history of AD, excessive alcohol intake, smoking and the use of psychotropic medication. Medications with positive effect on anxiety symptoms could influence the results in several ways. Moreover, some studies have associated the use of psychotropic medication with a higher risk of dementia (Shash et al., 2015), but other authors (Burke et al., 2016) argue that anxiolytics might neutralize the hazard of development AD associated with anxiety. The lost individuals in the sample were older and with lower MMSE scores, being theoretically at a higher risk of developing AD. However, we trust this has not influenced importantly the results. It is apparent that some individuals with incident AD may have been lost before they could be examined at follow-up, and therefore we do not know their anxiety status at baseline. The main reason for losses in this study has been the mortality, and could also be related to the low MMSE and associated disability. Previous reports have documented in older individuals the association of anxiety with cognitive decline (Gulpers et al, 2016), disability (Kang et al, 2017) and also with an increased mortality (Miloyan et al, 2016). Therefore, it might be expected that the onset of severe cognitive decline and probably AD, or the mortality would occur in a higher proportion of the anxiety cases than in the non-cases. Had these losses not happened, there would be more incident cases of AD among the anxiety cases. In such circumstances, the conclusions of this study would be reinforced. Finally, age at baseline was not included in the analysis as a

covariate. However, we used a different approach, with age as timescale to avoid biased estimates (Thiébaut & Bénichou, 2004).

ACKNOWLEDGEMENTS:

The authors acknowledge the contribution of the lay interviewers, senior medical students, and members of the ZARADEMP Workgroup who participated in the study.

Author contributions:

Javier Santabárbara participated in the study conceptualization and design, in the interpretation of data, drafting and revising critically the article for important intellectual content.

Beatriz Villagrasa participated in the study conceptualization and design, data acquisition, analysis and interpretation of data and drafting the article.

Raul Lopez-Anton participated in the study conceptualization and design, in the interpretation of data, drafting and revising critically the article for important intellectual content.

Beatriz Olaya participated in the interpretation of data and revising critically the article for important intellectual content.

Javier Bueno-Notivol participated in the data acquisition, interpretation of data and revising critically the article for important intellectual content.

Concepción de la Cámara participated in the data acquisition, interpretation of data and revising critically the article for important intellectual content.

Patricia Gracia-Garcia participated in the, data acquisition interpretation of data and revising critically the article for important intellectual content

Elena Lobo participated in the interpretation of data and revising critically the article for important intellectual content

Antonio Lobo participated in the supervision, project administration, founding acquisition, interpretation of data and revising critically the article for important intellectual content.

Conflict of Interest

We declare that C. De -la-Cámara has received financial support to attend scientific meetings from Janssen-Cilag, Almirall, Eli Lilly, Lundbeck, Rovi, Esteve, Novartis and Astrazeneca. Dr. P. Gracia - García has received Grant support from Janssen, AstraZeneca and the Ilustre Colegio de Médicos de Zaragoza; she has received Honorarium from AstraZeneca and Lilly; and she has received travel support from Lilly, Almirall, Lundbeck, Rovi, Pfizer and Janssen. J.M. None of these activities is related to the current project. For the remaining authors none were declared. BO's work is supported by the PERIS program 2016-2020 "Ajuts per a la Incorporació de Científics i Tecnòlegs" (grant number SLT006/17/00066), with the support of the Health Department from the Generalitat de Catalunya.

Conclusion

In conclusion, clinically significant anxiety, but not sub-clinical anxiety, was associated with AD risk in these study subjects, even after controlling for confounding factors. Although causal relations cannot be established with certainty, this finding may stimulate studies about the possibility of intervening on anxiety to prevent or delay the development of AD. Future research is also needed to understand mechanisms involved in the association of anxiety and AD risk.

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TABLES

Table 1. Baseline characteristics according to incident AD status

	No AD (N = 3968)	**Incident AD (N = 87)**	**p-value**
Age (years)	72.83 (9.03)	83.72 (7.13)	<0.001
Female sex	2168 (54.6%)	61 (70.1%)	0.004
Education			
Primary school	2960 (75.2%)	59(67.8%)	<0.001
High school or higher	681 (17.3%)	9 (10.3%)	
Civil status			
Married/in couple	2501 (63.2%)	27 (31.0%)	<0.001
Divorced/separated	57 (1.4%)	1 (1.1%)	
Widowed	1037 (26.2%)	57 (65.5%)	
Living alone	689 (17.4%)	12 (13.8%)	0.385
MMSE	27.27 (2.52)	24.46 (2.47)	<0.001
Anxiety	1,607 (40.5%)	38 (43.7%)	0.008
Subcase	85 (2.1%)	6 (6.9%)	
Case			
Depression	442 (11.1%)	13 (14.9%)	0.265
Disability			
Instrumental ADLs	479 (12.1%)	33 (37.9%)	<0.001
Basic ADLs	263 (6.6%)	14 (16.1%)	0.001
Health status (‘not good’)	2052 (51.7%)	49 (57.0%)	0.336
Vascular risk factors			
Hypertension	2692 (67.9%)	55 (63.2%)	0.354
Diabetes	491 (12.5%)	10 (11.6%)	0.814
Vascular disease	449(11.3%)	10 (11.5%)	0.959

Notes: Data are given as mean (standard deviation) or number (%).

p values were from "normal approximation" of t test with 4,053 *df* and Wald χ^2 test with 1 *df* (or 2 *df* for anxiety).

ADLs = activities of daily living; MMSE = Mini-Mental State Examination.

Table 2. Anxiety status and risk of AD

		Univariate Model		Multivariate Model	
Anxiety status at baseline	**No. (%) of AD incident cases**	**SHR (95% CI)[a]**	**p-value**	**SHR (95% CI)[a]**	**p-value**
Noncase (n=2321)	43 (1.8)	1	—	1	—
Subcase (n=1645)	38 (2.3)	1.07 (0.70-1.64)	0.760	1.19 (0.75-1.88)	0.460
Case (n=91)	6 (6.6)	**3.20 (1.39-7.40)**	**0.006**	**3.90 (1.59-9.60)**	**0.003**

Notes: SHR: Subdistribution Hazard Ratio. Bold entries mean the SHR is statistically significant.

[a]ReportedSHR of AD is related to noncases, CIs and p values related to SHR were from "normal approximation" of Wald χ^2 test with 1 *df*. Univariate Model include anxiety status and sex. Multivariate Model included terms from Model 1 plus sociodemographic characteristics (educational level, marital status, and living alone), medical risk factors (vascular disease, hypertension, and diabetes), health status, depression and cognitive status at baseline (MMSE).