Main text word count: 3807

Sex differences in longitudinal trajectories of cognitive aging in Zaragoza, Spain

Elena Lobo PhD[1, 2-3], Antonio Lobo M.D., PhD*[2-4], Patricia Gracia-García M.D., PhD[2-3, 4-5], Raúl López-Antón PhD[2-3, 6], Pedro Saz M.D.,PhD[2, 4], Concepción De la Cámara M.D.,PhD[2-3, 4, 7]

1 Department of Preventive Medicine and Public Health, Universidad de Zaragoza, 50009 Zaragoza, Spain; elobo@unizar.es (E.L.)

2 Instituto de Investigación Sanitaria de Aragón (IIS Aragón), 50009 Zaragoza, Spain; alobo@unizar.es (A.L.); pgraciag@salud.aragon.es (P.G.-G.); rlanton@unizar.es (R.L.-A.); psaz@unizar.es (P.S.); cdlcamara@salud.aragon.es (C.D.-l.-C.)

3 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, 28029 Madrid, Spain;

4 Department of Medicine and Psychiatry, Universidad de Zaragoza, 50009 Zaragoza, Spain

5 Psychiatry Service, Hospital Universitario Miguel Servet, 50009 Zaragoza, Spain

6 Department of Sociology and Psychology, Universidad de Zaragoza, 50001 Zaragoza, Spain

7 Psychiatry Service, Hospital Clínico Universitario, 50009 Zaragoza, Spain

*Correspondence: Antonio Lobo. Departamento de Medicina, Psiquiatría y Dermatología. Facultad de Medicina. Universidad de Zaragoza. C/Domingo Miral s/n, 50009, Zaragoza. alobo@unizar.es

Keywords: Sex differences, aging process, cognition, ZARADEMP Study

Abstract

Objectives: The objective of this study was to document the longitudinal trajectories of cognitive aging in a sample of cognitively healthy subjects of 55 years or older. The following differences between men and women were hypothesized: a) in the cognitive loss through aging, b) in the distinct trajectories identified; and c) in the predictors associated with the identified trajectories.

Design and setting: A 4-wave, population-based study in Zaragoza, Spain (1994-2006).

Participants: 2403 individuals aged 55+ years, cognitively healthy at baseline

Measurements: All participants had at least three measurements with the Mini-Mental State Examination (MMSE) . Validated Spanish versions of international instruments were used for assessment. Random effects linear panel regression model for analyzing differences by sex in MMSE scores through aging were performed, and growth mixture models (GMM) applied independently for each sex for modelling the longitudinal cognitive trajectories.

Results: Women showed lower mean MMSE scores in all phases and significantly higher loss in the MMSE from phases 2 to 3 and 3 to 4. The best fitting age-adjusted model of the cognitive trajectories was a 4-class growth mixture model in men and a 3-class in women. Education was a predictor of cognitive trajectories in both men and women. Dependence on iADLs and alcohol status were predictors only for men, and depression and diabetes only for women.

Conclusions: The identified differences by sex in cognitive trajectories and their associated factors suggest that men and women may require a different strategy when addressing cognitive aging.

Keywords: Sex differences, aging process, cognition, ZARADEMP Study

Introduction and Objectives

Recent evidence suggests that significant heterogeneity across individuals exists in the pattern of deterioration with age (1,2). The cautious analysis of cognitive paths (trajectories) may be crucial to understanding the complex and subtle variations across the lifespan (3,4). Some previous studies have identified distinct trajectories in individuals (1), and we have recently reported an age-adjusted model showing three heterogeneous classes of longitudinal changes in cognitive performance (5). Recent evidence also suggests that predictors of stable cognitive trajectories may differ from the factors related to trajectories of cognitive decline (1,5,6).

The relevance of studying the influence of sex on cognitive trajectories is also apparent. The urgent need "to bring sex and gender into the mainstream of modern medical research" has been underlined, since "the lack of appreciation for sex and gender differences harms both women and men" (7). In fact, differences by sex in the risk of several conditions have been reported (8–11). Regarding cognitive performance, while differences between men and women have been widely documented in cross-sectional studies (12), the effect of sex on the cognitive decline has not been clarified (13). McCarrey et al reported differences by sex, but other authors, including Ferreira et al in their systematic review could not find significant differences (4,14–16). However, none of the previous studies have independently addressed the intra-sex variability of cognitive trajectories. In the present paradigm of 'personalized' medicine and the need for actions tailored to individuals, it seems now timely to try to detect how men and women change their cognitive performance across aging, the rates of change, and the factors associated with the different trajectories, particularly the potentially modifiable factors.

The objective of this study was to test in a sample of cognitively healthy subjects of 55 years or older the hypotheses that differences between men and women would be found

in the loss of cognitive function through aging, in the cognitive trajectories, and the predictive factors associated with the identified trajectories.

Methods

The general methods of the ZARADEMP project, a longitudinal population-based study of dementia and depression in adults aged 55 years or older, conducted in Zaragoza, Spain, have been reported previously (17). For this study, four waves have been analyzed: Wave 1 (W1) starting in 1994 and the follow-up waves W2, W3, and W4 starting in 1997, 1999, and 2006, respectively. The study population consisted of a random, representative sample of the city (700,000 inhabitants), stratified with proportional allocation by age and sex, that included institutionalized individuals. Information on race and ethnicity was not collected. Only 0.51% of the inhabitants in the city were of foreign origin at the time the official census was gathered (18). The sampling technique and sampling size were determined as a function of type I and type II errors. We worked with a random sample from the census list, stratified by sex and age (5-year age categories). The design was also guided by the results in the previous Zaragoza Study (19) related to the expected prevalence rate, the negative predictive value of the screening instruments used, and the expected losses, specific for age and sex.

The study included 4,803 participants, with an overall participation rate of 79.5%. Individuals with dementia as well as those with "subsyndromal" dementia at baseline, according to the Geriatric Mental State (GMS), with its cognitive section and its Automated Geriatric Examination for Computer Assisted Taxonomy package (AGECAT) criteria (19), were excluded from the follow-up waves. The procedure comprised a two-phase case finding for dementia in each wave.

The Helsinki convention principles of written informed consent, privacy, and confidentiality have been maintained throughout the Project, and the Ethics Committee of the University of Zaragoza and the Fondo de Investigación Sanitaria (FIS) approved the study (CP16/2012, 19 September 2012), according to Spanish Law.

Assessment of cognitive function

Validated, Spanish versions of international instruments were used, including the cognitive section of the GMS and AGECAT, and the Mini-Mental State Examination, MMSE, measuring orientation in time and space, memory, attention, calculation, language, and visuoperception was used to document the cognitive trajectories (20,21).

In phase-1 of each wave, the lay interviewers (senior medical students) assessed the cognitive function in the elderly's home, and the data on each elderly were thoroughly reviewed by the research psychiatrists supervising individually the interviewers. In phase-2, the research psychiatrists re-examined, two months later, and blind to the results of Phase I, the probable cases of dementia. For this study, only the performance in the MMSE in phase 1 was used.

Other variables

Information on age, marital status, education, and health behaviors such as alcohol and smoking, were collected by interview at the baseline visit. Education was categorized as Low (Elementary School, complete or incomplete) and High (High School and/or University). Functional dependence was assessed using the History and Aetiology Schedule (HAS), disability scales (Katz's Index) for basic activities of daily living (bADLs), and Lawton and Brody scale for instrumental ADLs (iADLs). For the assessment of medical conditions, diabetes, and hypertension, the European Studies of Dementia (EURODEM) Risk Factors Questionnaire was used (22). Depression and anxiety syndromes were assessed utilizing the GMS interview and the respective sections

in the AGECAT computer system. After symptom assessment (AGECAT Stage I), a diagnosis of depression emerges from Stage II. In this stage, a computer program compares syndrome clusters (e.g., dementia, depression, anxiety) to reach a final diagnosis, recorded as either a diagnostic "subsyndromal" (confidence levels 1 and 2) or a diagnostic "case" (confidence levels 3). The "cases" level was used in this particular study.

Data analysis

Mean and standard deviation (SD) for continuous variables and proportions for categorical variables were used to describe baseline characteristics.

To test the hypothesis that differences between men and women would be found in the loss in cognitive function through aging, univariate Mann-Whitney U tests were used to compare mean MMSE scores and mean point loss in the MMSE from Wave 1 through Wave 4. Furthermore, random linear panel regression models using generalized least squares were estimated for the MMSE score with both sex and year-specific time random effects, including age, educational level, marital status, hypertension, depression, anxiety, dependency in iADLs, alcohol, tobacco use, Wave (1 through 4) and the interaction term of sex with each phase as potential confounders.

To examine trajectories of change over time in cognitive function, we used growth mixture models (GMM) (23,24), separately for men and women, modeling data from participants with different baseline ages and number of time points (25). This resulted in individuals being classified into clusters with similar trajectories according to their longitudinal data, assuming that individual differences in trajectories can be summarized by a finite set of different polynomial functions for age or time (26,27).

Using lcmm package of R software, linear and non-linear link functions, specifically Beta cumulative distribution functions and splines were used to estimate the best GMM for

men and for women. The time of the MMSE measurement, age at baseline, and the interaction between them were all incorporated in the models; including random effects in the time covariate. No other information was used to classify individuals into their clusters. All the individuals in the data set with at least three measurements of MMSE were included in the analyses. The best solution was selected after examining fit indices such as the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and the sample-size-adjusted BIC (SABIC), and considering the solution's interpretability and parsimony. Lower criterion values indicate better model fit. Additionally, based on Jung et al.'s criteria, a proportion of each class (no less than 1%) was considered (28).

In both subgroups of men and women, to compare the differences among the trajectory groups Chi-squared test, and one-way analysis of variance (ANOVA) with the Snedecor-F test were used. Multinomial logistic regression (MLR), with each class in each model as the referent (29), was applied to identify, separately for men and women, class membership predictors, including sociodemographic, physical, mental, and lifestyle variables. The best model was selected considering interpretability and parsimony. All analyses were implemented using R software (30).

Results

Baseline characteristics of the study sample by sex

A total of 1061 men and 1342 women were included in the analyses. As shown in Table 1, compared to men, women were older and were less frequently coupled and with a lower level of education, had more frequent hypertension, depression, anxiety, dependency in

iADLs, and less frequently drank alcohol or smoked. The MMSE scores for women were lower in all waves than in men.

Cognitive trajectories by sex

From Wave 1 to Wave 4, the MMSE score loss in men was 1 point and 1.5 points in women (p = 0.005) (Table 1). The adjusted random linear panel regression model showed that from wave 2 to wave 3 and from wave 3 to wave 4 the mean MMSE score loss was 0.5 points higher for women compared to men (ß= 0.54, Std Error= 0.17, p= 0.002; and ß=0.56, Std Error= 0.21, p= 0.008, respectively). No significant differences between both sexes were seen in the mean MMSE score loss from wave 1 to wave 2 (ß=0.30, Std Error= 0.17, p=0.086).

Supported by the differences by sex found in the cognitive trajectories, we then studied the intra-sex variability of cognitive aging independently in males and females. Figure 1 shows the trajectories resulting from the best-fit growth mixture models for men and for women. Each sample (men and women) mean curves, as well as the details of MMSE mean scores for each class and wave, are included in the same figure.

In men (Figure 1), the best fitting age-adjusted model of the cognitive trajectories was a 4-class growth model (AIC= 13729,91; BIC= 13814,35; SABIC= 13760,36; maximum log-likelihood= -6847,96) in which 28.8% (305) and 52.9% (562) of men were included in the classes 3-Stable High and 4-Stable Medium, respectively (turquoise and purple), with no decline during follow-up. Class 2-Declining High comprised 4.8% (51) of men (green) who declined on average 4.1 points in MMSE scores from wave 1 to wave 4. The rest of the men, 13.5% (143), were categorized in the worst trajectory (class 1-Declining Low, in red) and showed a faster decline with a difference between baseline and final MMSE score of 6.5 points on average.

In the women sample, the best-fitting age-adjusted model was the 3-class growth mixture model (AIC= 19413,32; BIC= 19486,14; SABIC= 19441,67; maximum log-likelihood= -9692,66) (Figure 1). Half of the women sample (50.2%), categorized in class 3-Stable High (blue), showed no cognitive decline in follow-up as shown MMSE scores, waves 1 to 4. Class 2-Stable Medium (green) included participants with a slight decline during the 4 waves; and the rest (2.4%) belonged to class 1-Declining (red) and showed a faster decline, with a difference between final and baseline MMSE score of 16.8 points on average.

Clustering of baseline characteristics by sex

Tables 2 and 3 show the sociodemographic, health, and lifestyle characteristics at baseline, according to the cognitive trajectory classes. In men, the four trajectory groups significantly differed in education level, marital status, depression, dependency, and alcohol status. No differences were found in HTN, Diabetes, Anxiety, and Smoking Status (Table 2). In women, the three trajectory groups significantly differed in education level, diabetes, depression, dependency on iADLs, and smoking status. The groups did not differ in marital status, HTA, Anxiety, dependency in bADLs, and Alcohol Status (Table 3).

Multivariable-adjusted models of Predictors of Class Membership, by sex

Tables 4 and 5 show the multinomial logistic regression analyses for men. In model A, compared with Class 3-Stable-High), individuals with a higher level of education were less likely to appear in classes 1 (OR= 0.11) and 4 (OR= 0.24) (Table 4). It was more likely to be in class 1 for individuals with dependency in iADLs (OR= 4.48) and in class 4 (OR= 2.99). Similarly, it was more likely to be in class 2 for occasional drinkers (OR=3.11); and in class 4 for ex-drinkers (OR= 1.68) (Table 4).

In model B, compared with class 1, having a higher level of education increased the probability of being (besides class 3 already mentioned) in class 2 (OR=6.14) and, in class 4 (OR=2.30); and occasional drinkers were more likely included in class 2 (OR=4.33) (Table 5).

In model C, compared with class 2, subjects with higher level of education (OR= 0.38) and occasional drinkers (OR= 0.33) were less likely included in class 4 (Table 5).

There were no individuals single, depressed, or dependent in bADLS in class 2 (Table 2). Therefore, extreme OR values and excessively wide 95% CI's were observed related to these three variables in the multivariate analysis when comparing class 2 with the rest of the classes. Since the three variables provided poor statistical information, they were excluded from the analysis, which resulted in similar results for all the models, the exclusion being preferred in terms of parsimony and interpretability. For women, the multinomial logistic regression analyses (Table 6) showed in model D that, compared with class 3-Stable-High, women with a higher level of education were less likely to appear in the Stable-Medium (class 2) group (OR= 0.16). Those with diabetes (OR= 1.79) and depression (OR= 1.31) were more likely to be included in the same class 2 group. The same trend was observed when comparing females in class 1 with the reference class 3, for diabetes and depression, but the associations were not statistically significant. No differences were observed in model E when comparing class 1 with class 2 (Table 6). iADLs and smoking status did not remain associated in the multivariate analyses and were excluded from the models.

Discussion and Conclusions

This study supports the hypothesis about sex differences in cognitive trajectories in the adult and older populations. First, mean MMSE global scores in Waves 1 through 4 were significantly higher in men, and the loss on MMSE points was significantly higher in women from the Second Wave to the end of the follow-up. Second, distinct cognitive trajectories have been found in both men (4 categories) and women (3 categories) and differences by sex in the grouping of trajectories throughout the aging process have been identified. Third, 81.7% of men, and only 50.2% of women, did not deteriorate cognitively in 12 years, the curve of decliners in women being sharper than in their counterparts. And, fourth, predictive factors were also different by sex for the trajectories identified: while education was a predictor of cognitive trajectories in both men and women, dependence on iADLs and alcohol status were predictors only for men; and depression and diabetes were predictors only for women.

In support of the relevance of analyzing independently the results in men and women, the results in this study both for the trajectories and the predictive factors were different than in our previous study, when the analysis was performed in the combined sample of men and women (5). To our knowledge, this is the first study capturing the intra-sex variability of cognitive aging in each sex using the GMM methodology. These analyses acknowledge the heterogeneity in the trajectories over time but also permit the identification of subpopulations with similar patterns of change within each sample of men and women.

The available information directly related to sex differences in cognitive trajectories in healthy aging is limited and still debatable. Ferreira et al 2014, in a systematic review, suggested that the rate of decline is similar between the sexes until the age of 80 years, and some later studies have similarly concluded (15,16,31). However, some recent studies report that women show more rapid cognitive function decline with aging (32,33)

and, on the contrary, McCarrey et al, and Zaninotto et al, observed that older women have greater resilience to and less rapid age-related cognitive decline than their male counterparts (4,34). It is difficult to compare our results with these previous reports since they provided a mean pattern of change for each sex, but none has analyzed separately GMM trajectories.

There is also limited information on predictors of class membership, and the same described difficulties exist to compare the results of these previous studies with ours. Yaffe et al included only women in their study, which focused on mortality prediction; they reported that factors such as educational level, depression, and diabetes were associated with cognitive decline, but this part of their study was limited to bivariate statistical analysis (35). Zaninotto et al provided more information, and following multifactorial analysis found that depression and alcohol use were associated with cognitive decline in some cognitive domains, but only in men; and factors such as smoking and limited physical activity were associated with a more rapid decline in some cognitive domains, both in men and women (34). Reas et al, observed that for both sexes, higher education was associated with slower rates of decline on the MMSE (31). However, these previous studies only reported a mean pattern of change for each sex. In our study, the multifactorial analysis shows that the best cognitive trajectory (class 3) in both sexes is observed in individuals with high educational levels. In men, a high educational level did differentiate between those in class 3 (Stable High) and class 1 (Declining Low); and between those in class 4 (Stable Medium) and class 1. It also differentiated between those who decline gradually (class 2) and those who decline more steeply (class 1). Among women, a high educational level did differentiate between those in class 3 (Stable High) and class 2 (Stable Medium), which included participants with mild MMSE decline.

These results may suggest prevention strategies related to cognitive performance. The importance of stimulating a high educational level is more apparent among women, in view that among men there is a group highly educated who has a trajectory (class 2), with a significant, although gradual decline (4.1 MMSE points). Nevertheless, our results may also have some implications for preventing severe cognitive decline in men: among them, the probability of membership in class 1 is very low in individuals with high education (OR= 0.11). The same trend was observed among women, although the association did not reach statistical significance, probably because of the small number of individuals in that group (class 1). Indeed, potential preventive programs should pay attention to the fact that the frequency of low education in women in the trajectories with cognitive decline (classes 1 and 2) was very high (93.7% and 94.8% respectively) and significantly higher than in the trajectory without decline (class 3); and the fact that the steepest decline was observed precisely among women. Prevention of the deleterious effect of low education has a particular interest in cities with a high proportion of the population with low educational levels, especially among women, such as Zaragoza (36). Since the educational level has improved dramatically in Spain in the last decades (37), this study may be one of the last opportunities to study the influence of low educational levels in this country, and the findings may inspire similar research in other cultures.

Other differences by sex were observed in the factors associated with cognitive trajectories. In women, but not in men, both depression and diabetes were associated with the group with mild cognitive decline (class 2), and the same, non-significant trend was observed related to class 1 with faster decline, when compared with the group of women in class 3 (Stable High).

While initiatives to prevent cognitive decline by treating depression (38) and diabetes (39) are increasingly observed in the literature, this paper is the first founding evidence

to support the programs separately for women. This is remarkable and has public health implications since diabetes and particularly depression are common in the adult and older population, as shown in this study, in which the prevalence of clinically significant depression in the full sample of women was 13.3% (40).

Among men, functional dependence in iADLs differentiated between those in class 3 (Stable High) and those in class 1 (Declining Low) and in class 4 (Stable Medium) who were more frequently dependent. Therefore, these findings may support programs to fight dependence in men but not in women. The results on alcohol status in men, in coincidence with a previous report in the full sample, do not support recommending occasional drinking to prevent cognitive decline (41), as this factor was associated with the decliners high group (class 2) when compared to the stable groups (classes 3 and 4).

Some authors have attempted to explain differences between sexes, which are not understood yet. Biological mechanisms have been advanced, including hormonal, immunological, or metabolic differences (42) and genetic risk factors (43). Nevertheless, a range of environmental exposures in early life, lifetime style, socio-cultural, and other contextual factors should be considered (13–15). While some authors suggest that social conditions have disproportionately improved for women more than men in recent decades (4,44), the baseline study shows that women were particularly disadvantaged related to education.

Among the strengths of this study, we consider the GMM methodology implemented; the large sample size, derived from a representative population sample, so that the results are generalizable to people living in Zaragoza, a rather typical large city in Spain; the screening procedure to recruit individuals who were cognitively healthy at baseline, which was stringent; differently from most previous studies in this area, using screening type of questionnaires, depression in this study was assessed with the GMS-AGECAT

instruments, methods considered to be valid to detect clinically significant, treatable depression in older people (45); and age at baseline was considered an important potential confounder for the identification of patterns and was included and controlled for in the data modeling; and education level was controlled for in the comparison of cognitive trajectories between both sexes and when comparing the intra-sex trajectories independently for men and for women.

There are several limitations to consider. We trust general issues such as selective dropout in longitudinal studies and missing data in some variables do not substantially modify the main results and conclusions. Since this study focused on the global cognitive deficit, we cannot extend our findings to particular cognitive domains. The stringent exclusion of subcases of dementia at baseline impedes the observation of trajectories in individuals with non-severe cognitive deficits. It might be argued that individual variability was not accounted for, but the GMM methodology grouped individuals in more than two categories allowing a more informative analysis than the classical comparison of cases and no cases of cognitive decline or dementia. The data related to one of the declining groups in men (Class 2) needs cautious interpretation because of the low number of subjects. Finally, we cannot discard the influence of factors uncontrolled in this study and the fact that some baseline modifiable factors studied might have changed during follow-up.

In conclusion, differences by sex identified in cognitive performance, cognitive loss, and the number, grouping, and predictors of trajectories throughout the aging process suggest that sex differences in the strategies to address cognitive aging may be required.

Author Contributions: E. L. conceptualized and designed the study, prepared and analyzed the data, and drafted the manuscript. A. L. designed the general ZARADEMP project and secured funding, formulated the research questions, supervised the data collection, and helped write the manuscript. P. GG. contributed to the implementation of the study and assisted with writing the manuscript. R. L.-A. analyzed data and revised the manuscript. P. S. contributed to the design and implementation of the study and the training of lay interviewers, supervised the data collection, and revised the manuscript. C.D.l.C. contributed to the design and implementation of the study and the training of lay interviewers, supervised the data collection, and assisted with writing the manuscript.

Declaration of competing interest

E. Lobo has received honorarium from University of Granada. A. Lobo had a consultancy with Janssen and received financial support to attend scientific meetings from Eli Lilly, Bial and Janssen. P. Gracia-García received financial support to attend scientific meetings from Lundbeck, Angelini, and Exeltis. C. De-la-Cámara received financial support to attend scientific meetings from Janssen, Almirall, Lilly, Lundbeck, Rovi, Esteve, Novartis, Astrazeneca, Pfizer and Casen Recordati. None of these activities were related to the current project. For the remaining authors, none was declared.

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

Grant support and financial disclosure: This work was 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, 12/02254, 16/00896, PI/19/01874, PI/19/00948, G03/128); from the Fondo Europeo de Desarrollo Regional (FEDER) of the European Union "Una manera de hacer Europa" (Project number PI16/00896) and from Gobierno de Aragón (grant B15_17R).

Data Sharing Statement: The data presented in this study are available upon reasonable request from the corresponding author and approval of the funder.

Previous presentation: Part of this work was presented at the XL Annual Meeting of the Sociedad Española de Epidemiología (SEE) and XVII Congress of the Associação Portuguesa de Epidemiologia (APE) (San Sebastián, Spain) in September 2022.

References

1. Wu Z, Phyo AZZ, Al-harbi T, et al. Distinct Cognitive Trajectories in Late Life and Associated Predictors and Outcomes: A Systematic Review. *J Alzheimer's Dis Reports*. 2020;4(1):459-478. doi:10.3233/adr-200232

2. Calderón-Larrañaga A, Hu X, Haaksma M, et al. Health trajectories after age 60: the role of individual behaviors and the social context. *Aging (Albany NY)*. 2021;13(15):19186-19206. doi:10.18632/aging.203407

3. World Health Organization O. *World Report on Ageing and Health*.; 2015. https://apps.who.int/iris/bitstream/handle/10665/186463/9789240694811_eng.pdf?sequence=1&isAllowed=y. Accessed February 25, 2019.

4. McCarrey AC, An Y, Kitner-Triolo MH, et al. Sex differences in cognitive trajectories in clinically normal older adults. *Psychol Aging*. 2016;31(2):166-175. doi:10.1037/pag0000070

5. Lobo E, Gracia-García P, Lobo A, et al. Differences in Trajectories and Predictive Factors of Cognition over Time in a Sample of Cognitively Healthy Adults, in Zaragoza, Spain. *Int J Environ Res Public Health*. 2021;18(13). doi:10.3390/IJERPH18137092

6. McFall GP, McDermott KL, Dixon RA. Modifiable Risk Factors Discriminate Memory Trajectories in Non-Demented Aging: Precision Factors and Targets for Promoting Healthier Brain Aging and Preventing Dementia. *J Alzheimer's Dis*. 2019;70(s1):S101-S118. doi:10.3233/JAD-180571

7. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet (London, England)*. 2020;396(10250):565-

582. doi:10.1016/S0140-6736(20)31561-0

8. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet (London, England)*. 2016;388(10046):761-775. doi:10.1016/S0140-6736(16)30506-2

9. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. *BMJ*. 2018;363. doi:10.1136/BMJ.K4247

10. McCartney G, Mahmood L, Leyland AH, et al. Contribution of smoking-related and alcohol-related deaths to the gender gap in mortality: evidence from 30 European countries. *Tob Control*. 2011;20(2):166-168. doi:10.1136/TC.2010.037929

11. DeMeo DL, Ramagopalan S, Kavati A, et al. Women manifest more severe COPD symptoms across the life course. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3021-3029. doi:10.2147/COPD.S160270

12. Compère L, Piolino P. Does the brain have a gender? A literature review in younger and older adults. *Geriatr Psychol Neuropsychiatr Vieil*. 2014;12(4):404-412. doi:10.1684/PNV.2014.0496

13. Bloomberg M, Dugravot A, Dumurgier J, et al. Sex differences and the role of education in cognitive ageing: analysis of two UK-based prospective cohort studies. *Lancet Public Heal*. 2021;6(2):e106-e115. doi:10.1016/S2468-2667(20)30258-9

14. Ostan R, Monti D, Gueresi P, et al. Gender, aging and longevity in humans: an

update of an intriguing/neglected scenario paving the way to a gender-specific medicine. *Clin Sci (Lond)*. 2016;130(19):1711-1725. doi:10.1042/CS20160004

15. Ferreira L, Ferreira Santos-Galduróz R, Ferri C, et al. Rate of cognitive decline in relation to sex after 60 years-of-age: a systematic review. *Geriatr Gerontol Int*. 2014;14(1):23-31. doi:10.1111/GGI.12093

16. Chadjikyprianou A, Hadjivassiliou M, Papacostas S, et al. The Neurocognitive Study for the Aging: Longitudinal Analysis on the Contribution of Sex, Age, Education and APOE ε4 on Cognitive Performance. *Front Genet*. 2021;12. doi:10.3389/FGENE.2021.680531

17. Lobo A, Saz P, Marcos G, et al. *The ZARADEMP Project on the Incidence, Prevalence and Risk Factors of Dementia (and Depression) in the Elderly Community: II. Methods and First Results*. Vol 19.; 2005.

18. Escalona Orcao AI, Escolano Utrilla S. Los trabajadores extranjeros en la provincia de Zaragoza. *Geographicalia*. 1993;(30):155. doi:10.26754/OJS_GEOPH/GEOPH.1993301816

19. Lobo A, Saz P, Marcos G, et al. The prevalence of dementia and depression in the elderly community in a southern European population. The Zaragoza study. *Arch Gen Psychiatry*. 1995;52(6):497-506. http://www.ncbi.nlm.nih.gov/pubmed/7771920.

20. 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. doi:10.1016/0022-3956(75)90026-6

21. Lobo A, Saz P, Marcos G, et al. Revalidation and standardization of the cognition

mini-exam (first Spanish version of the Mini-Mental Status Examination) in the general geriatric population. *Med Clin (Barc)*. 1999;112(20):767-774.

22. Launer LJ, Hoffman A. Studies on the incidence of dementia: the European perspective. *Neuroepidemiology*. 1992;11(3):127-134. doi:10.1159/000110922

23. Muthén B, Shedden K. Finite mixture modeling with mixture outcomes using the EM algorithm. *Biometrics*. 1999;55(2):463-469. doi:10.1111/j.0006-341X.1999.00463.x

24. Ram N, Grimm KJ. Methods and Measures: Growth mixture modeling: A method for identifying differences in longitudinal change among unobserved groups. *Int J Behav Dev*. 2009;33(6):565-576. doi:10.1177/0165025409343765

25. Proust-Lima C, Philipps V, Liquet B. Estimation of extended mixed models using latent classes and latent processes: The R package lcmm. *J Stat Softw*. 2017;78(1):1-56. doi:10.18637/jss.v078.i02

26. Nagin DS. Analyzing developmental trajectories: A semiparametric, group-based approach. *Psychol Methods*. 1999;4(2):139-157. doi:10.1037/1082-989X.4.2.139

27. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6:109-138. doi:10.1146/annurev.clinpsy.121208.131413

28. Jung T, Wickrama KAS. An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. *Soc Personal Psychol Compass*. 2008;2(1):302-317. doi:10.1111/j.1751-9004.2007.00054.x

29. Park S, Kwon E, Lee H. Life course trajectories of later-life cognitive functions: Does social engagement in old age matter? *Int J Environ Res Public Health*.

2017;14(4). doi:10.3390/ijerph14040393

30. R: The R Project for Statistical Computing. https://www.r-project.org/. Accessed April 18, 2023.

31. Reas ET, Laughlin GA, Bergstrom J, et al. Effects of Sex and Education on Cognitive Change Over a 27-Year Period in Older Adults: The Rancho Bernardo Study. *Am J Geriatr Psychiatry*. 2017;25(8):889-899. doi:10.1016/J.JAGP.2017.03.008

32. Nooyens ACJ, Wijnhoven HAH, Schaap LS, et al. Sex Differences in Cognitive Functioning with Aging in the Netherlands. *Gerontology*. 2022;68(9). doi:10.1159/000520318

33. Levine DA, Gross AL, Briceño EM, et al. Sex Differences in Cognitive Decline Among US Adults. *JAMA Netw open*. 2021;4(2). doi:10.1001/JAMANETWORKOPEN.2021.0169

34. Zaninotto P, Batty GD, Allerhand M, et al. Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. *J Epidemiol Community Health*. 2018;72(8):685-694. doi:10.1136/jech-2017-210116

35. Yaffe K, Peltz CB, Ewing SK, et al. Long-term Cognitive Trajectories and Mortality in Older Women. *J Gerontol A Biol Sci Med Sci*. 2016;71(8):1074-1080. doi:10.1093/gerona/glw003

36. The situation in Spain of functional illiteracy – Kaffi project EU. https://kaffi-project.eu/the-situation-in-spain-of-functional-illiteracy/. Accessed September 28, 2022.

37. Albert C. Higher education demand in Spain: The influence of labour market signals and family background. *High Educ*. 2000;40(2):147-162. doi:http://dx.doi.org/10.1023/A:1004070925581

38. Dafsari FS, Jessen F. Depression-an underrecognized target for prevention of dementia in Alzheimer's disease. *Transl Psychiatry*. 2020;10(1). doi:10.1038/S41398-020-0839-1

39. Palta P, Carlson MC, Crum RM, et al. Diabetes and Cognitive Decline in Older Adults: The Ginkgo Evaluation of Memory Study. *J Gerontol A Biol Sci Med Sci*. 2017;73(1):123-130. doi:10.1093/GERONA/GLX076

40. Gracia-García P, de-la-Cámara C, Santabárbara J, et al. Depression and incident Alzheimer disease: the impact of disease severity. *Am J Geriatr Psychiatry*. 2015;23(2):119-129. doi:10.1016/j.jagp.2013.02.011

41. Lobo E, Dufouil C, Marcos G, et al. Is there an association between low-to-moderate alcohol consumption and risk of cognitive decline? *Am J Epidemiol*. 2010;172(6):708-716. doi:10.1093/aje/kwq187

42. Barha CK, Falck RS, Skou ST, et al. Personalising exercise recommendations for healthy cognition and mobility in aging: time to address sex and gender (Part 1). *Br J Sports Med*. 2021;55(6):300-301. doi:10.1136/BJSPORTS-2020-102864

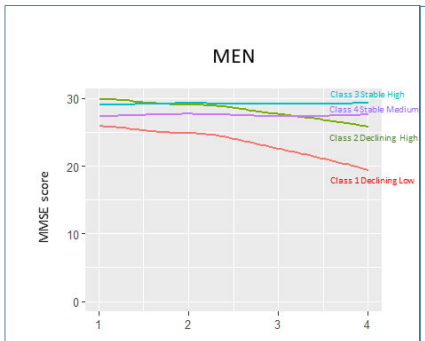
43. Wang YTT, Pascoal TA, Therriault J, et al. Interactive rather than independent effect of APOE and sex potentiates tau deposition in women. *Brain Commun*. 2021;3(2). doi:10.1093/BRAINCOMMS/FCAB126

44. Weber D, Skirbekk V, Freund I, et al. The changing face of cognitive gender differences in Europe. *Proc Natl Acad Sci U S A*. 2014;111(32):11673-11678.

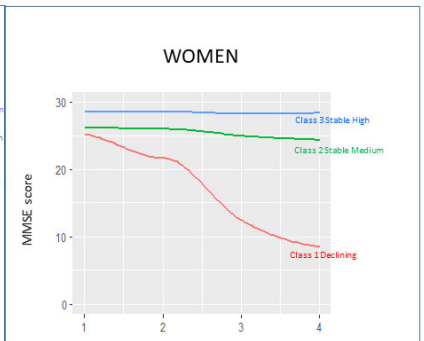
doi:10.1073/PNAS.1319538111

45. Schaub RT, Linden M, Copeland JRM. A comparison of GMS-A/AGECAT, DSM-III-R for dementia and depression, including subthreshold depression (SD) - Results from the Berlin Aging Study (BASE). *Int J Geriatr Psychiatry*. 2003;18(2):109-117. doi:10.1002/gps.799

Figure 1. Growth mixture model estimated means of MMSE (cognitive trajectories) over 12 years of follow-up for men and women: ZARADEMP study.



Class	MMSE mean scores (SD)			
	Wave 1	Wave 2	Wave 3	Wave 4
1-Declining Low	25.9 (3.7)	24.9 (4.4)	22.6 (6.0)	19.44 (8.3)
2-Declininggn High	30.0 (0.2)	29.1 (1.0)	27.7 (1.4)	25.9 (2.9)
3-Stable High	29.1 (1.0)	29.4 (0.9)	29.2 (1.0)	29.4 (1.0)
4-Stable Medium	27.4 (1.7)	27.8 (1.6)	27.4 (1.8)	27.7 (2.0)



Class	MMSE mean scores (SD)			
	Wave 1	Wave 2	Wave 3	Wave 4
1-Declining	25.3 (2.9)	21.7 (5.5)	12.5 (9.9)	8.5 (8.9)
2-Stable Medium	26.3 (2.3)	26.0 (2.5)	25.0 (3.3)	24.4 (4.8)
3-Stable High	28.5 (1.4)	28.6 (1.4)	28.3 (1.9)	28.4 (1.7)

Table 1. Baseline characteristics of the study sample by sex, MMSE mean scores and mean point loss at follow-up.

	MEN (N= 1061)	WOMEN (N=1342)	p-value*
Age	69.8 (8)	70.6 (8)	0.004
High Education	275 (26.1%)	191 (14.3%)	0.000
Marital status			
Single[a]	70 (6.6%)	181 (13.5%)	
Coupled	903 (85.3%)	726 (54.3%)	0.000
Widowed	86 (8.1%)	431 (32.2%)	
HTN	668 (63%)	942 (70.2%)	0.001
Diabetes	121 (0.7%)	161 (12%)	0.874
Depression	61 (5.7%)	318 (23.7%)	0.000
Anxiety	18 (1.7%)	77 (5.7%)	0.000
iADLs	60 (5.7%)	122 (9.1)	0.003
bADLs	37 (3.5%)	65 (4.8%)	0.255
Alcohol			
Exdrinker	198 (18.7%)	57 (4.2%)	
Habitual	447 (42.1%)	130 (9.7%)	0.000
Never	338 (31.9%)	1115 (83.1%)	
Ocassional	76 (7.2%)	40 (3%)	
Smoking status			
Smoker and Ex-smoker	759 (71.6%)	97 (7.2%)	0.000
MMSE in phase 1	27.8 (2.2)	27.4 (2.2)	0.000
Follow-up:			
MMSE in phase 2	27.9 (2.5)	27.2 (2.6)	0.000
MMSE in phase 3	27.3 (3.3)	26.4 (4.1)	0.000
MMSE in phase 4	27.2 (4.4)	26.3 (4.8)	0.000

Loss in MMSE Wave 1 to 4	1 (4.2)	1.5 (4.4)	0.005

Note: HTN: Hypertension; iADLs: instrumental Activities of Daily Living; bADLs: basic Activities of Daily Living. MMSE: Mini-Mental Status Examination. [a]Single, divorced or monk/nun. *Chi^2 and Man-Whitney U tests

Table 2. Baseline characteristics of men, total sample and classes 1-4.

	Class 1 N=143 (13.5%)	**Class 2** N=51 (4.8%)	**Class 3** N=305 (28.8%)	**Class 4** N=562 (53.0%)	**p-value***
Age	70.5 (8.4)	68.3 (7)	69 (7.5)	70.2 (8.2)	0.079
Education Level					
Low	130 (90.9)%	31 (60.8%)	158 (51.8%)	459 (81.7%)	<0.001
High	12 (8.4%)	19 (37.3%)	145 (47.5%)	99 (17.6%)	
NA	*1 (0.7%)*	*1 (2.0%)*	*2 (0.7%)*	*4 (0.7%)*	
Marital Status					
Single[a]	12 (8.4%)	0 (0%)	28 (9.2%)	30 (5.3%)	0.001
Coupled	112 (78.3%)	48 (94.1%)	265 (86.9%)	478 (85.1%)	
Widowed	18 (12.6%)	3 (5.9%)	12 (3.9%)	53 (9.4%)	
NA	*1 (0.7%)*	*0 (0%)*	*0 (0%)*	*1 (0.2%)*	
HTN	102 (71.3%)	32 (62.8%)	192 (63%)	342 (60.9%)	0.161
NA	*0 (0%)*	*0 (0%)*	*0 (0%)*	*2 (0.4%)*	
Diabetes	14 (9.8%)	9 (17.7%)	33 (10.8%)	65 (11.6%)	0.498
NA	*2 (1.4%)*	*0 (0.0%)*	*1 (0.3%)*	*4 (0.7%)*	
Depression	9 (6.3%)	0 (0%)	11 (3.6%)	41 (7.3%)	0.034
NA	*13 (9.1%)*	*0 (0.0%)*	*2 (0.7%)*	*12 (2.1%)*	
Anxiety	3 (2.1%)	0 (0.0%)	4 (1.3%)	11 (2%)	0.678
NA	*140 (97.9%)*	*0 (0.0%)*	*0 (0%)*	*551 (98%)*	
iADLs	14 (9.8%)	1 (2.0%)	7 (2.3%)	38 (6.8%)	0.003
NA	*2 (1.4%)*	*0 (0.0%)*	*0 (0%)*	*1 (0.2%)*	
bADLs	9 (6.3%)	0 (0%)	4 (1.3%)	24 (4.3%)	0.015
NA	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*	*1 (0.2%)*	
Alcohol					

Ex-drinker	30 (21%)	7 (13.7%)	42 (13.8%)	119 (21.2%)	
Habitual	63 (44.1%)	24 (47.1%)	122 (40%)	238 (42.4%)	0.014
Never	44 (30.8%)	12 (23.5%)	113 (37.1%)	169 (30.1%)	
Ocassional	6 (4.2%)	8 (15.7%)	27 (8.9%)	35 (6.2%)	
NA	*0 (0%)*	*0 (0%)*	*1 (0.3%)*	*1 (0.2%)*	
Smoking status					
Non-smoker	43 (30.1%)	16 (31.4%)	93 (30.5%)	149 (26.5%)	0.548
Smoker and Ex-smoker	100 (69,93%)	35 (68.6%)	211 (69.2%)	413 (73.5%)	
NA	*0 (0,00%)*	*0 (0%)*	*1 (0.3%)*	*0 (0%)*	

Note: *NA:* Not available. HTN: Hypertension; iADLs: instrumental Activities of Daily Living; bADLs: basic Activities of Daily Living. [a]Single, divorced or monk/nun. *Chi^2 and F tests

Table 3. Baseline characteristics of women, total sample and classes 1-3.

	Class 1 N=32 (2.4%)	Class2 N=636 (47.4%)	Class 3 N=674 (50.2%)	p-value*
Age	70.7 (7.9)	71 (7.9)	70.2 (8)	0.193
Education Level				
Low	30 (93.8%)	603 (94.8%)	513 (76.1%)	<0.001
High	2 (6.3%)	28 (4.4%)	161 (23.9%)	
NA	0 (0%)	5 (0.8%)	0 (0%)	
Marital status				
Couple	17 (53.1%)	333 (52.4%)	376 (55.8%)	
Single[a]	5 (15.6%)	73 (11.5%)	103 (15.3%)	0.056
Widowed	10 (31.3%)	227 (35.7%)	194 (28.8%)	
NA	0 (0%)	3 (0.5%)	1 (0.2%)	
Hypertension	25 (78.1%)	461 (72.5%)	456 (67.7%)	0.091
NA	0 (0%)	1 (0.2%)	0 (0,00%)	
Diabetes	4 (12.5%)	101 (15.9%)	56 (8.3%)	<0.001
NA	0 (0%)	7 (1.1%)	3 (0.5%)	
Depression	10 (31.3%)	163 (25.6%)	145 (21.5%)	0.022
NA	5 (15.6%)	42 (6.6%)	8 (1.2%)	
Anxiety	2 (6.3%)	38 (6%)	37 (5.5%)	0.924
NA	0 (0%)	0 (0%)	0 (0%)	
iADLs	7 (21.9%)	64 (10.1%)	51 (7.6%)	0.011
NA	0 (0%)	1 (0.2%)	0 (0%)	
bADLs	2 (6.3%)	33 (5.2%)	30 (4.5%)	0.769
NA	0 (0%)	1 (0.2%)	1 (0.2%)	

Alocohol				
Ex-drinker	0 (0%)	31 (4.9%)	26 (3.9%)	0.158
Habitual	2 (6.3%)	56 (8.8%)	72 (10.7%)	
Never	29 (90.6%)	537 (84.4%)	549 (81.5%)	
Ocassional	1 (3.1%)	12 (1.9%)	27 (4%)	
NA	0 (0%)	0 (0%)	0 (0%)	
Smoking status				
Non-smoker	32 (100%)	604 (95%)	609 (90.4%)	0.002
Smoker and Ex-smoker	0 (0%)	32 (5%)	65 (9.6%)	
NA	0 (0%)	0 (0%)	0 (0%)	

Note: *NA:* Not available. iADLs: instrumental Activities of Daily Living; bADLs: basic Activities of Daily Living. [a]Single, divorced or monk/nun. *Chi^2 and F tests.

Table 4. Multinomial Logistic Regression of Predictors of Class Membership in men. Model A.

	Model A (Reference Class 3-Stable High)					
	Class 1		**Class 2**		**Class 4**	
	OR	95% CI	OR	95%CI	OR	95%CI
Education[a]	**0.11**	**0.06 – 0.20**[e]	0.65	0.35 – 1.20	**0.24**	**0.18 – 0.33**[f]
iADLs dependency	**4.48**	**1.69 – 11.83**[d]	0.93	0.11 – 7.77	**2.99**	**1.28 – 6.99**[c]
Alcohol[b]						
Ex-drinker	1.51	0.82 – 2.79	1.61	0.58 – 4.44	**1.68**	**1.07 – 2.62**[c]
Habitual	1.32	0.81 – 2.15	1.97	0.92 – 4.22	1.29	0.92 – 1.82
Occasional	0.72	0.27 – 1.93	**3.11**	**1.13 – 8.51**[c]	1.01	0.56 – 1.83

Note: iADLs: instrumental Activities of Daily Living; [a]Reference: Illiterate/Primary; [b]Reference: Never; [c]p-value <0.05; [d]p-value <0.01; [e]p-value <0.001.

Table 5. Multinomial Logistic Regression of Predictors of Class Membership in men. Models B and C

	Model B (Reference Class 1-Decliners Low)						Model C (Reference Class 2-Decliners High)					
	Class 2		Class 3		Class 4		Class 1		Class 3		Class 4	
	OR	95% CI	OR	95%CI	OR	95%CI	OR	95% CI	OR	95%CI	OR	95%CI
Education[a]	**6.14**[e]	**2.68 – 14.08**	**9.51**	**5.03 – 17.96**[e]	**2.30**	**1.23 – 4.33**[d]	**0.16**	**0.07 – 0.37**[e]	1.55	0.83 – 2.88	**0.38**	**0.20 – 0.70**[d]
iADLs dependency	0.21	0.03 – 1.64	**0.22**	**0.08 – 0.59**[d]	0.67	0.35 – 1.28	4.82	0.61 – 38.15	1.08	0.13 – 8.99	3.22	0.43 – 24.18
Alcohol[b]												
Ex-drinker	1.07	0.37 – 3.11	0.66	0.36 – 1.23	1.11	0.65 – 1.89	0.94	0.32 – 2.72	0.62	0.23 – 1.71	1.04	0.39 – 2.78
Habitual	1.50	0.66 – 3.40	0.76	0.47 – 1.23	0.98	0.63 – 1.52	0.69	0.29 – 1.15	0.51	0.24 – 1.08	0.65	0.31 – 1.38
Occasional	**4.33**	**1.22 – 15.35**[c]	1.39	0.52 – 3.74	1.41	0.56 – 3.59	**0.23**	**0.07 – 0.82**[c]	**0.32**	**0.12 – 0.88**[c]	**0.33**	**0.12 – 0.88**[c]

Note: iADLs: instrumental Activities of Daily Living; [a]Reference: Illiterate/Primary; [b]Reference: Never; [c]p-value <0.05; [d]p-value <0.01; [e]p-value <0.001.

Table 6. Multinomial Logistic Regression of Predictors of Class Membership in women. Models D and E.

	Model D (Reference Class 3-Stable High)				**Model E (Reference Class 1-Declining)**			
	Class 1		Class 2		Class 2		Class 3	
	OR	95% CI	OR	95%CI	OR	95% CI	OR	95%CI
Education [a]	0.27	0.08 – 1.10	**0.16**	**0.11 – 0.23**[d]	0.60	0.13 – 2.67	3.71	0.87 – 15.91
Diabetes	1.65	0.66 – 4.17	**1.79**	**1.32 -2.43**[c]	1.08	0.37 – 3.22	0.60	0.20 – 1.82
Depression	2.04	1.04 – 4.01	**1.31**	**1.05 – 1.65**[b]	0.64	0.29 – 1.44	0.49	0.22 – 1.10

Note: [a]Reference**:** Illiterate/Primary. [b]p-value <0.05; [c]p-value <0.01; [d]p-value <0.001.