Impact of Individual and Neighborhood dimensions of Socioeconomic Status on the Prevalence of Mild Cognitive Impairment over Seven-Year Follow-Up

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Abstract. IMPORTANCE: There is strong evidence about the association between low socioeconomic status (SES) and higher risk of dementia. However, it has not been conveniently addressed so far the role of SES on the incidence of Mild Cognitive Impairment (MCI) which is considered a prodromal stage of latter dementia. OBJECTIVE: To examine the impact of individual and neighborhood dimensions of SES, as well as their interaction, on the risk of developing MCI in a sample of older adults that were followed-up for seven years. DESIGN, SETTING, AND PARTICIPANTS: Data from the Vallecas Project cohort, an ongoing community-based longitudinal study for early detection of cognitive impairment and dementia, were used to build two indices of SES namely individual and neighborhood, as well as a global SES as a combination of both, and to investigate their effects on MCI conversion by means of a multivariate-adjusted Cox proportional hazard model. MAIN OUTCOMES AND MEASURES: Based on data referred to as individual-level (one's educational attainment, occupation, parent's level of education) and neighborhood-level (district's income, unemployment rate, housing price, percentage of people with no formal qualifications, with higher education, and with white-collar employs) different composite measures of SES were built and quartiles were considered for further analyses. MCI diagnoses were agreed between neurologists and neuropsychologists at consensus meetings. RESULTS: 1180 participants aged 70 years and older were enrolled in this study (mean age at baseline, 74.9 years; 63.5% females). Of these, 199 cases of MCI (16.9%) were diagnosed at any point of the follow-up. The individual and neighborhood dimensions of SES played different roles in the dynamics of the MCI occurrence through ageing. Most importantly, the risk of developing MCI was almost double for lower SES quartiles when compared to the highest one. CONCLUSIONS: The incidence of MCI in older adults was related to both individual characteristics and socioeconomic context. Public health strategies should be holistic and focus not only on promoting the classical individual preventive measures, but also on reducing social inequalities as a means of fostering healthy ageing and reducing dementia burden.

INTRODUCTION

In the last years social phenomena have been incorporated into the scope of neuroscience, especially neuroepidemiology, to better explain individual

behavior, dysfunction and disease. The socioeconomic status (SES), that was a mere covariate in statistical analyses, has become a topic of interest for researchers in its own right (Farah, 2017). SES is a complex construct that reflects the overall position in the society

of a person. Thus, SES is often operationalized as a combination of education, occupation, income, and other related familiar and neighborhood characteristics such as exposure to violence, pollution, parental and health care or cognitively stimulating environment (Krieger, Williams, & Moss, 1997). From the perspective of the public health, understanding how SES interacts with both healthy and pathological human development is a crucial issue.

Although in general terms SES could be conceptualized as a continuum from worst to best off in which those who are better off have access to more material and non-material resources, SES is typically divided into levels to refer to the places where an individual can be situated (e.g. quintiles, quartiles, etc.). The utility of SES lies precisely in its ability to place a person in a continuum in relation to the others. Thanks to this, it has been possible to analyze the role of SES as a predictor in a broad range of health variables. In particular, higher SES have been associated with lower rates of some physical conditions such as coronary disease, diabetes, stroke, cancer, and arthritis (Adler & Stewart, 2010), or psychiatric illnesses such as depression or anxiety (Kessler et al., 2005; Lorant et al., 2003). Regarding cognition, it has been demonstrated an association between SES and cognitive performance in adults across lifespan, independent of individual demographic and health characteristics (Besser, McDonald, Song, Kukull, & Rodriguez, 2017; Lorant et al., 2003; Weng et al., 2018). There has also been evidenced an association between SES and the incidence of dementia (Cadard et al., 2018; Nakahori et al., 2018), as well as with mortality (Åberg Yngwe, Kondo, Hägg, & Kawachi, 2012; Russ et al., 2013; van de Vorst, Koek, Stein, Bots, & Vaartjes, 2016). However, it has not been conveniently addressed so far the role of SES on the incidence of Mild Cognitive Impairment (MCI) which is considered a prodromal stage of latter dementia (Jack et al., 2018; Petersen, 2004).

Socioeconomic factors could affect health at different times in the lifespan, at distinct levels (e.g. individual, familiar, or area-based), and through different causal pathways (e.g. by determining exposures, vulnerability, or direct physiological effects) (Braveman et al., 2005). In research practice SES is often indirectly estimated in terms of individual factors, specifically education and occupation, or in terms of area-based characteristics such as the context or the neighborhood in which a person lives. Therefore, two dimensions of SES namely individual SES (ISES) or neighborhood SES (NSES) could be differentiated according to some nuances.

The main aim of the present study is to examine the impact of ISES and NSES, as well as their interaction, on the risk of developing MCI over time in a sample of

people over 70 years of age who have been followed-up for seven years.

METHODS

Participants

The Vallecas Project is an ongoing community-based longitudinal investigation for early detection of cognitive impairment and dementia (Olazarán et al., 2015). The study began in October 2011 and currently 6 complete waves of data collection have been performed over a follow-up period of 7 years. At baseline 1,180 community-dwelling individuals aged 70 and over were enrolled. All participants have undergone a detailed assessment protocol at every wave including medical history, neurological and neuropsychological examination, biochemical and genetic blood test, MRI scan, as well as information on lifestyle, well-being and socioeconomic circumstances. The complete assessment at every visit has been usually carried out within four hours with convenient breaks. Further details on the Vallecas Project are described in eMethods section (Supplement).

Ethical approval for the Vallecas Project was granted by the Research Ethics Committee of the Carlos III Institute of Health. Written informed consent was obtained from all the participants.

Study variables

Socioeconomic indicators

Different characteristics of SES were measured at baseline to ascertain two composite measures of SES:

1. ISES was estimated according to the following three variables:
 - Educational attainment: (0) no formal qualifications; (1) primary education; (2) secondary education; and (3) higher education.
 - Occupation: (0) non-qualified/homemaker; (1) manual work; (2) clerical work; (3) graduate/technician work; and (4) managerial positions.
 - The highest level of education reached by parents: (0) no formal qualifications; (1) primary education; and (2) secondary or higher education.
2. NSES was based on six variables associated with neighborhoods that were retrieved from the Department of Statistics of Madrid City Council:
 - Average annual net income: (0) up to €24,999; (1) €25,000-€49,999; and (2) €50,000 and over.

- Percentage of people with no formal qualifications.
- Percentage of people with higher education.
- Percentage of white-collar workers.
- Unemployment rate.
- Housing price (€/square meter).

Each individual and neighborhood variable was firstly standardized to facilitate comparisons. Then, we calculated a z-score for every participant both in the ISES and in the NSES dimensions. Finally, the z-score distribution was split into quartiles where Q1 represented the worst-off and Q4 the best-off.

Clinical diagnoses

Every participant was independently diagnosed taking into account age, gender, functional information, and neuropsychological scores. Cognitive diagnoses were agreed between neurologists and neuropsychologists at consensus meetings. In all cases, cognitively healthy subjects had to obtain a score of 0 in the global Clinical Dementia Rating (CDR) (Hughes, Berg, & Danziger, 1982). Criteria from the National Institute on Aging-Alzheimer's Association (NIA-AA) were used to diagnose MCI (Albert et al., 2011).

Covariates

We considered age at conversion to MCI, gender, and ApoE genotyping as potential confounders for cognitive impairment. ApoE genotype was studied with total DNA isolated from peripheral blood following standard procedures. Genotyping of polymorphisms (rs429358 and rs7412) was performed by Real-Time PCR (Calero, Hortigüela, Bullido, & Calero, 2009). ApoE was coded 1 for the ϵ 4-carriers, and 0 for non-carriers. Males and ϵ 4 carriers were used as reference groups.

Statistical analyses

We performed a preliminary analysis of the individual and neighborhood variables considered in this study. In all cases, associations between categorical variables were analyzed using Fisher or Pearson's χ^2 test. The comparisons between cognitively unimpaired individuals and MCI were performed with the non-parametric Wilcoxon test due to the differences in sample sizes and to the non-adjustment to the parametric assumptions of most dependent variables. A complementary analysis of demographic, cognitive, clinical, anthropometric, and lifestyle variables at baseline to find out their relationships to SES is described in the Supplementary material.

Both ISES and NSES were treated as four-level independent variables defined by the quartile; upper quartile was always used as the reference group in the analyses. The association between ISES, NSES, and the last cognitive diagnosis registered in the follow-up for every participant was exploratory studied by means of contingency tables. Moreover, to analyze longitudinally the relationship between ISES, NSES, and conversion rate to MCI, two multivariate-adjusted Cox proportional hazard models were obtained. All the results were presented as hazard ratio (HR) with a 95% confidence interval (CI). Time to event was calculated as date of entry into the study to date of MCI diagnosis or the end of the study period. Age at MCI onset, gender, and ApoE genotype were introduced as covariates. The Schoenfeld residual test was used to test the proportional hazards assumption of the models. Finally, to study the interaction between the individual and the neighborhood dimensions of SES upon the MCI conversion, we created a new variable by crossing lower and upper quartiles of the ISES and the NSES. This resulted in a global SES (GSES) dimension with 4 categories ordered hypothetically from the highest ($Q_{\text{gSES}}1$) to the lowest ($Q_{\text{gSES}}4$) risk of MCI conversion. Then, a final third Cox proportional hazard model was obtained for GSES.

All analyses were conducted in R version 3.5.1. (R Development Core Team, 2008). We used 2-sided significance tests for all analyses, with statistical significance set at P Value < 0.05.

RESULTS

The sample included in this study was composed of 1,180 individuals (median follow-up duration, 5 years; range, 1-7 years). The baseline diagnoses were 1,088 cognitively normal individuals, 83 MCI cases and 9 dementia patients. Table 1 shows the baseline characteristics of the sample.

A preliminary analysis only considering cognitively unimpaired and MCI subjects showed statistically significant differences in relation to all individual and neighborhood characteristics. A strong association was also found between ISES and NSES quartiles and both diagnostic groups whereby the upper quartiles showed a lower percentage of MCI cases than the lower quartiles (Table 1). A complementary examination of a large set of baseline variables of diverse nature was also conducted. The results showed a straight and linear trend always in favor of higher levels versus lower levels of SES in a large set of baseline variables of diverse nature (eTable 1 in the Supplement). Even controlling for the gender effect similar results were found what indicate that gender is not a confounder factor (eTable 2 and eTable 3 in the Supplement).

Table 1. Baseline characteristics of the cohort by quartiles of individual and neighborhood socioeconomic status

Characteristics, Mean (SD)	Total (n=1180)	Control (n=1088)	MCI (n=83)	Dementia (n=9)	P Value ^a
Demographics					
Age, y	74.9 (3.9)	74.7 (3.9)	77.2 (3.7)	79.9 (3.0)	< .001
Female, No. (%)	750 (63.6)	695 (63.9)	48 (57.8)	7 (77.8)	.288
Individual-level variables					
Education, No. (%)					
No formal qualifications	240 (20.4)	202 (18.6)	35 (42.2)	3 (33.3)	< .001
Primary education	360 (30.6)	325 (29.9)	29 (34.9)	6 (66.7)	
Secondary education	279 (23.7)	268 (24.7)	11 (13.3)	0 (0.0)	
Higher education	299 (25.4)	291 (26.8)	8 (9.6)	0 (0.0)	
Occupation, No. (%)					
Non-qualified/homemaker	322 (33.5)	295 (32.5)	26 (51.0)	1 (50.0)	.006
Manual work	222 (23.1)	206 (22.7)	15 (29.4)	1 (50.0)	
Clerical work	149 (15.5)	143 (15.7)	6 (11.8)	0 (0.0)	
Graduate/technician work	210 (21.9)	206 (22.7)	4 (7.8)	0 (0.0)	
Managerial positions	58 (6.0)	58 (6.4)	0 (0.0)	0 (0.0)	
Parent's education, No. (%)					
No formal qualifications	249 (25.8)	225 (24.7)	23 (44.2)	1 (50.0)	.004
Primary education	515 (53.4)	490 (53.8)	24 (46.2)	1 (50.0)	
Secondary or Higher	200 (20.7)	195 (21.4)	5 (9.2)	0 (0.0)	
Neighborhood-level variables					
Average annual net income, €	35051 (13854)	35385 (14096)	31113 (7845)	31020 (7845)	.004
Proportion of no qualifications	20.3 (9.7)	20.0 (9.7)	23.6 (8.8)	22.9 (8.2)	.001
Proportion of higher education	29.8 (18.1)	30.3 (18.1)	23.8 (15.9)	24.9 (15.3)	.001
Proportion of white-collar workers	45.7 (15.9)	46.2 (16.0)	40.4 (13.0)	39.2 (15.1)	.002
Unemployment rate	9.0 (2.6)	9.0 (2.6)	9.9 (2.4)	9.5 (2.1)	.001
Housing price, €/m ²	2374 (1103)	2403 (1115)	2044 (919)	2046 (736)	.003
ISES, No. (%)					
Q1	292 (24.8)	251 (23.1)	37 (44.6)	4 (44.4)	< .001
Q4	290 (24.5)	258 (23.7)	27 (32.5)	5 (55.6)	
Q3	305 (25.9)	293 (27.0)	12 (14.5)	0 (0.0)	
Q4	293 (24.8)	286 (26.2)	7 (8.4)	0 (0.0)	
NSES, No. (%)					
Q1	296 (25.1)	257 (23.6)	36 (43.4)	3 (33.3)	< .001
Q4	298 (25.3)	277 (25.5)	19 (22.9)	2 (22.2)	
Q3	292 (24.7)	271 (24.9)	17 (20.5)	4 (44.4)	
Q4	294 (24.9)	283 (26.0)	11 (13.3)	0 (0.0)	

Abbreviations: ISES, individual socioeconomic status; NSES, neighborhood socioeconomic status.

^aSince the small sample size of the dementia group, variables were compared only between Control and Mild Cognitive Impairment. Fisher and Pearson's χ^2 test for categorical and non-parametric Wilcoxon for ordinal variables tests were used. ISES an NSES quartiles follow an ordinal distribution so that the upper quartile (Q4) corresponded to the best off, while the lower one (Q1) were referred to the worst off.

Figure 1 shows the percentage of individuals who were diagnosed as cognitively unimpaired throughout the visits at the Vallecas Project by ISES (bars in blue) and NSES (bars in red). As expected the percentage of cognitively intact subjects was decreasing over the follow-up, thus increasing the number of MCI patients: a total of 199 subjects with MCI (16.9%) were

identified. Interestingly, the age at MCI onset for lower quartiles (Q1-Q2) was earlier than for upper ones (Q3-Q4) both for ISES (77.1 vs 79.8 years old) and for NSES (76.8 vs 80.5 years old). Moreover, the distribution of the MCI prevalence with age is different for ISES and NSES as shown in Figure 2.

a) Cognitively unimpaired subjects by Individual Socioeconomic Status (ISES)

b) Cognitively unimpaired subjects by Neighborhood Socioeconomic Status (NSES)

Figure 1. Individuals diagnosed as cognitively unimpaired throughout the visits at the Vallecas Project

The association between socioeconomic status and the last cognitive diagnosis registered for each participant was analyzed. We then found significant statistical differences for ISES (χ^2 , 20.12; $P = .003$), with a greater percentage of MCI cases in lower versus upper quartiles especially at the ages of 75-85. However, even though a similar pattern of results was

observed for NSES until the age of 80, no clear association was obtained with clinical diagnoses (χ^2 , 7.08; $P = .314$). As showed in Figure 2b, this outcome was mainly due to an unexpected decrease in the prevalence of MCI in the lower NSES quartiles in comparison to upper ones in which prevalence continued to rise.

a) Prevalence of Mild Cognitive Impairment by Individual Socioeconomic Status (ISES)

b) Prevalence of Mild Cognitive Impairment by Neighborhood Socioeconomic Status (NSES)

Figure 2. Mild Cognitive Impairment prevalence throughout ageing

Abbreviations: MCI, Mild Cognitive Impairment; Q, quartile.

To better illustrate the rate of MCI progression according to age, the initial quartiles were collapsed in two categories representing lower (Q1-Q2) and upper (Q3-Q4) quartiles. As expected, there is an overall increase of MCI prevalence with age for both ISES (2a) and NSES (2b); lower quartiles show a major percentage of MCI diagnoses than upper quartiles, especially for ISES and between 70-80 years. However, some differences can be appreciated when inspecting both figures. While lower and upper quartiles in ISES follow the same trend with respect to MCI, in NSES there is a decrease in the percentage of individuals with MCI from the age of 85 onwards. This phenomenon is associated with the attrition of the cohort which is more marked in lower quartiles probably due to several factors intrinsically associated to NSES such as lower expectancy of life, major rate of disability, or worse general health status.

Finally, the unadjusted Cox proportional hazard models longitudinally confirmed the results that lower quartiles had an increased risk of progression to MCI compared to upper ones. Specifically, the analysis of the interaction of individual and neighborhood dimensions showed that GSES Q1 and Q2 had about a 60-67% increased risk of MCI progression compared to GSES Q4. Kaplan-Meier plots showed clear differences in risk by Q1 and Q2 after 7 years of follow-up (Figure

3). On the other hand, adjusted Cox regression models were also conducted to control the influence of age at MCI onset, gender, and ApoE genotype upon GSES and its association with conversion to MCI. As shown in Table 2, compared to GSES Q4 the multivariate adjusted HRs were 1.83 (95% CI, 1.04-3.21) for GSES Q1 and 1.74 (95% CI, 1.06-2.86) for GSES Q2. GSES Q3 did not differ from Q4.

Table 2. Cox proportional hazard regression models of conversion rate to MCI

	Model 1^a		Model 2^b		Model 3^c	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Q4^d	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Q3	1.62 (0.96-2.73)	.071	1.05 (0.62-1.77)	.860	1.26 (0.30-5.39)	.755
Q2	1.71 (0.95-3.07)	.076	1.15 (0.69-1.92)	.587	1.74 (1.06-2.86)	.030
Q1	1.95 (1.12-3.40)	.018	1.07 (0.62-1.84)	.803	1.83 (1.04-3.21)	.036

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; Q, quartile.

^aModel 1: adjusted for age at MCI onset, gender, ApoE, and ISES.

^bModel 2: adjusted for age at MCI onset, gender, ApoE, and NSES.

^cModel 3: adjusted for age at MCI onset, gender, ApoE, and GSES.

^dQuartiles follow an ordinal distribution so that the upper quartile (Q4) corresponded to the best off, while the lower one (Q1) were referred to the worst off.

DISCUSSION

Our study aimed to examine the relative impact of individual and neighborhood dimensions of SES, as well as their interaction, on the risk of developing MCI in a sample of older adults that were followed-up for seven years. Overall, our results support the idea that there is a definite relationship between SES and risk of developing MCI in elderly people.

In our sample a moderate-high overlapping between ISES and NSES was found. This overlapping seems to be mediated by individual factors such as educational attainment. What can be inferred from this finding is that there was very little social promotion in our cohort born between 1925 and 1944. This segment of population suffered directly both the effects of the Spanish civil war (1936-1939) and the economic consequences of the postwar period. If a person was born in a disadvantaged environment then that person was more likely to remain in a deprived environment because of the scarcity of opportunities in relation to education as an element in reducing social inequalities. We hypothesize that this phenomenon is gradually being alleviated in next generations thanks to the improvement of the socioeconomic context and the universal access to education. The normalization of international relationships of Spain with the introduction of the parliamentary democracy after Franco's dictatorial regime has played an important role in shortening social distances in our country.

Our results show an increase in the prevalence of the MCI as a function of age for ISES and NSES which is consistent with other similar studies (Kim et al., 2017; Wee et al., 2012). For both SES dimensions, subjects in lower quartiles showed a higher rate of MCI than those in upper ones, especially between 70 and 80 of age. However, as depicted in Figure 2, from 80 onwards there was a different trend that affected lower quartiles of both SES dimensions: while in ISES the prevalence of MCI increased, in NSES there was a decrease. This outcome could be associated with the attrition to our study which mainly affects to persons that lived in deprived areas. The reasons that can explain such high attrition include factors intrinsically associated with NSES such as greater morbidity and earlier mortality (Kopp, Skrabski, Réthelyi, Kawachi, & Adler, 2004), major rate of physical disability and worse general health status (Veenstra, 2000), and greater stress and worse psychological well-being (Everson-Rose et al., 2011; Präg, Mills, & Wittek, 2016). Ultimately, Figure 2 reflects the importance of considering the conjunction of ISES and NSES dimensions to better explain the dynamics in the occurrence of the MCI.

The impact of GSES on the conversion rate to MCI during 7-year follow-up showed that the risk of developing cognitive impairment was almost double for lower quartiles than for upper ones. According to our results, elderly people with low-GSES have 60-67% increased risk of developing MCI than those with high-GSES. Thus, low-GSES may be considered a risk factor for MCI. These data are consistent with previous findings in the literature (Goldbourt, Schnaider-Beeri, &

Davidson, 2007; Kim et al., 2017) and could have several explanations. First, high-SES is usually related to wealth what is directly associated with the possibility of consuming products, goods and services that provide positive effects upon health and cognition (Diez Roux & Mair, 2010; Rosso et al., 2016). Second, high-SES is also related to cognitive enriched environments which favor the growth of social networks, emotional support, major sense of social effectiveness, and better general health condition (Berkman, Glass, Brissette, & Seeman, 2000; Kim & Park, 2015). Third, NSES is able to influence individual's health through a series of environmental variables that include exposures to crime or pollution, proximity to services such as hospitals or parks, etc. (Sharkey & Faber, 2014). Fourth, low-NSES have often more chronic stressors and fewer resources compared to high-NSES, and this might lead to restricted opportunities for social and cognitive stimulation as well as less access to good health services (Barnes, Mendes de Leon, Wilson, Bienias, & Evans, 2004; Ertel, Glymour, & Berkman, 2008). Fifth, as a result of difficulty making ends meet for individuals with low-SES, they tend to be more depressed and stressed which may lead to faster ageing (Kondo, 2012). Finally, high-SES might not only improve life conditions but also facilitate the ability and motivation to participate in activities that improve the well-being which indirectly may help to prevent cognitive disorders (Sattler, Toro, Schönknecht, & Schröder, 2012).

Figure 3. Kaplan-Meier survival curves for rates of Mild Cognitive Impairment by Global Socioeconomic Status quartiles

Survival curves based on Cox regression analysis comparing cumulative Mild Cognitive Impairment (MCI) incidence in subjects cognitively normal at baseline by each Global Socioeconomic Status (GSES) quartile. The figure is derived from a model that is adjusted for age of diagnostic, sex and APOE genotype. Duration of follow-up is truncated at 7 years. Q1 and Q2 show the highest risk of conversion to MCI compared with Q4.

In terms of the cognitive reserve hypothesis (Stern, 2002, 2012), and based on our results, we propose that the two SES dimensions considered in this study play complementary roles in brain and cognitive functioning. On the one hand, ISES which was defined as a combination of three factors -educational attainment, occupation and parents' the highest level of education- appears to be associated with the concept of cognitive reserve. High-ISES would be related to a greater acquisition of knowledge and effective cognitive strategies from childhood to adulthood. In addition, high-SES individuals tend to have healthy behaviors which include read and practice more cultural and leisure activities which also helps maintain cognitive reserve capacity (Pampel, Krueger, & Denney, 2010). This would allow explaining why MCI is more prevalent for low-ISES than high-ISES through the lifespan as cognitive reserve is able to compensate the neuropathological damages related to cognitive ageing. On the other hand, NSES, a composite score based on characteristics of the neighborhood in which a person lives, seems to impact further on brain reserve. The best living conditions (e.g. diet, cognitive stimulation, access to health services, etc.) that are supposedly associated with high-NSES, especially in the early life, would allow for greater neurocognitive and brain development (Hackman, Farah, & Meaney, 2010). In any event, early experiences like amount and quality of education could override the influences of the neighborhood context, being more important in predicting later cognitive performance (Glymour & Manly, 2008).

The findings of this study have two important implications. First, the dynamics and prevalence of MCI through ageing is conditioned by the SES of individuals. This has implications for health care professionals as far as they should take into account both the individual characteristics and the socioeconomic context to better understand MCI. Second, it is crucial to go beyond the classical perspective on individual preventive strategies for dementia based on lifestyle modifications (e.g. diet, physical activity or cognitive training). We consider policies that targeting the reduction of social inequalities also offer a means of promoting healthy ageing in society. For example, policies aimed at reducing disparities in wealth or favoring access to educational or health resources for the most disadvantaged people. The understanding of how SES relates to cognitive function could help policy-makers to design strategies for prevention and intervention for older adults (Hackman et al., 2010; Meyer et al., 2018).

Strengths

To our knowledge, this is the first longitudinal study that examines separately the influence of the two dimensions of SES on the prevalence of MCI, a

prodromal stage that is considered to increase the probability of suffering latter dementia (Jack et al., 2018; Petersen, 2004). Through a 7-year follow-up of a well-characterized cohort of older adults that has been tracked annually, we have been able to demonstrate the association of ISES and NSES on cognitive diagnoses. Moreover, we have benefited from the availability of official and accurate statistical data about neighborhoods made available to the general public by the Department of Statistics of Madrid City Council.

Limitations

There is a lack of longitudinal information on individuals who discontinued the study. Therefore, we cannot be certain of the mortality rate of the entire cohort and all we can do is speculate on the reason for the loss of subjects in NSES Q1 and Q2 from approximately 80 years of age. Moreover, since no specific information on biomarkers is available in our study, we cannot determine the etiology of each MCI case. It ought to be noted that diagnosis of MCI is multifactorial; a set of candidate causes, both reversible and non-reversible, could play a role in the diagnosis (Petersen et al., 2014).

Conclusions

In a well-characterized Spanish cohort of older adults, the risk of MCI was associated with the two dimensions of SES, and specifically the effect of ISES was consistently higher. However, since ISES and NSES have different effects mediated by age on cognitive impairment, the interplay of both SES dimensions must be considered. Public health strategies should focus not only on promoting the classical individual preventive measures (e.g. through lifestyle modification), but also on reducing social inequalities (e.g. by favoring access to educational and health resources for the most disadvantaged people) as a means to foster healthy ageing and reduce dementia burden.

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Author contributions

Drs Fernández-Blázquez, Del Ser, and Gómez-Ramírez had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fernández-Blázquez, Ávila-Villanueva, Del Ser, Gómez-Ramírez.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Fernández-Blázquez, Noriega-Ruiz.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Fernández-Blázquez

Study supervision: Del Ser, Gómez-Ramírez.

Conflict of interest disclosures

The authors report no conflicts of interest relevant to the manuscript.

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Role of the funder/sponsor

The funders had no role in design and conduct of the study; collection, management, statistical analysis, and interpretation of the data; preparation, drafting, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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SUPPLEMENTARY ONLINE CONTENT

eMethods

The Vallecas Project for early detection of AD is the most ambitious community-based study for healthy aging in Spain.(Olazarán et al., 2015) The project is an ongoing single-center, observational, longitudinal cohort study that is carried out at the Queen Sofia Foundation Alzheimer Center by a multidisciplinary team of researchers from the CIEN Foundation. The main objective of the Vallecas Project is to identify, through monitoring progression of the cohort, the best combination of features, clinical and others that are informative about developing cognitive impairment in the future. The participants were recruited between 2011 and 2013 in Madrid (Spain) and were home-dwelling volunteers, aged 70 to 85 years, without relevant psychiatric, neurologic or systemic disorders. After signing informed consent, they undertake a yearly systematic clinical assessment including medical history, neurological and neuropsychological exam, blood collection and brain MRI. The study was approved by the Ethics Committee of the Carlos III Institute of Health.

For the purposes of our study we have analyzed the association of ISES and NSES with the following set of variables collected in the Vallecas Project at baseline:

1. Demographics:
 - 1.1. Age, years.
 - 1.2. Education: No. (%) of people with higher education.
 - 1.3. Occupation: No. (%) of white-collar workers.
 - 1.4. Gender: No. (%) of females.
 - 1.5. ApoE: No. (%) of $\epsilon 4$ -carriers.
2. Clinical:
 - Hypertension: No. (%) of people with hypertension.
 - Cholesterol: No. (%) of people with high levels of cholesterol.
 - Diabetes: No. (%) of people with diabetes.
 - Stroke: No. (%) of people with stroke with no apparent cognitive or motor impairment.
 - Smoking: No. (%) of people smokers or ex-smokers.
 - Depression: No. (%) of people with depressive symptoms.
 - Auditory deficit: No. (%) of people with corrected or uncorrected hearing impairment.
 - Visual deficit: No. (%) of people with corrected or uncorrected visual impairment.
3. Cognitive status:
 - Mini Mental Status Examination (MMSE): total score (range, 0-30); high scores reflect better cognitive performance.
 - Free and Cued Selective Reminding Test (FCSRT): number of words correctly recalled both immediately (range, 0-48) and delayed (range, 0-16); high scores reflect better verbal memory performance.
 - Semantic fluency: number of animals mentioned in a minute (no range); high scores reflect better language performance.
 - Digit-Symbol: total number of correctly transposed symbols in one minute (no range); high scores reflect faster processing speed and better attentional performance.

- Functional Activities Questionnaire (FAQ): total score (range, 0-33); high scores reflect a higher level of dependence on managing activities of daily living.
 - Clinical Dementia Rating (CDR): sum of boxes score (range, 0-18); high scores reflect greater severity of cognitive impairment.
4. Neuroimaging:
- Gray matter volume, cm^3 .
 - White matter volume, cm^3 .
5. Motor exam
- Up & Go test: time in seconds that takes a person to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down.
 - Taps right hand: number of taps in one minute performed by opening and closing the thumb and index fingers of the right hand.
 - Taps left hand: number of taps in one minute performed by opening and closing the thumb and index fingers of the left hand.
6. Lifestyle
- EuroQol-5D (EQ-5D): total score of health status (range, -0.654 – 1.000).
 - Physical activity (walking, swimming, gym): (1) almost never; (2) sometimes; and (3) usually.
 - Manual activity (handicrafts, bobbin lace, bricolage): (1) almost never; (2) sometimes; and (3) usually.
 - Leisure activity (going to cinema, theatre, concerts, exhibitions, conferences): (1) almost never; (2) sometimes; and (3) usually.
 - Creative activity (painting, drawing, writing, composing music): (1) almost never; (2) sometimes; and (3) usually.
 - Social activity (going out for a walk, dancing, coffee): (1) almost never; (2) sometimes; and (3) usually.
 - Reading (books, newspapers, magazines): (1) almost never; (2) sometimes; and (3) usually.
 - Information and Communications Technology (ICT) use (computer, mobile phone, surf the web): (1) almost never; (2) sometimes; and (3) usually.
7. Diet
- Fruit consumption during the last week: (0) 0 days; (1) 1-2 days; (2) 3-5 days; and (3) 6-7 days.
 - Vegetables consumption during the last week: (0) 0 days; (1) 1-2 days; (2) 3-5 days; and (3) 6-7 days.
8. Anthropometric
- Weight, kg.
 - Height, cm.
 - Body Mass Index (BMI), kg/m^2 .

We performed a preliminary analysis with the above mentioned variables to find out their distribution and potential relationships with SES. Both ISES and NSES were treated as four-level independent variables defined by the quartile. Upper quartile was always used as the

reference group in the analyses. Moreover, since the percentage of females was disproportionately distributed according to ISES and NSES quartiles, the analyses were repeated separately for males and females to control for the gender effect upon the results. In all cases, associations between categorical variables were analyzed using the Pearson's χ^2 test. The comparisons between groups were performed with the non-parametric Kruskal-Wallis tests due to the differences in sample size and to the non-adjustment to the parametric assumptions of most variables. Bonferroni correction was used in order to minimize the number of false positives when performing multiple comparisons.

eResults

eTable 1 summarizes the baseline characteristic by ISES and NSES quartiles. An expected a straight and linear trend was always found in favor of higher levels versus lower levels of SES in a large set of baseline variables of diverse nature: (1) demographics: age, education, occupation, and gender; (2) clinical: smoking, depression, and auditory deficit; (3) cognitive performance: global cognition, episodic memory, semantic fluency, processing speed, and clinical impression; (4) MRI: grey and white matter volumetry; (5) motor: up & go and tapping with both hands; (6) lifestyle: quality of life, as well as frequency of engagement in everyday activities such as leisure, creative, social, reading, and ICT use; and (7) anthropometrics: weight, height and body mass index (BMI). These results are compatible with those already found in the literature relating high-SES with larger brain sizes,(Waldstein et al., 2017) greater thicknesses of cortical gray matter and even brain's functional network organization,(Chan et al., 2018) better cognitive performance,(Lyu & Burr, 2016; Marden, Tchetgen Tchetgen, Kawachi, & Glymour, 2017) and richer life-styles such as more high-quality food(Mayén, Marques-Vidal, Paccaud, Bovet, & Stringhini, 2014) or less smoking habits.(Eibner & Evans, 2005) The repetition of these analyses separately for males and females gave similar results indicating that gender is not a confounder factor (eTable 2 and eTable3).

There is an overlapping of the significant variables in both SES; however differences between upper and lower quartiles are greater in ISES than in NSES. eFigure 1 shows the magnitude of those differences. Moreover, while significant differences may be found between Q2 and Q3 in SES, we did not obtain so clear differences in NSES. The magnitude of the effect produced by ISES was greater for the majority of variables than that produced by NSES, except for some biological variables such as volumetry of gray and white matter, BMI and auditory deficits (eFigure 1). Moreover, differences between the four ISES quartiles were also greater than between the four NSES quartiles. These findings would suggest that there is a well-established pattern of linear trend between the four ISES quartiles but the same pattern is not found regarding the NSES quartiles.

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eTable 1. Baseline characteristics of the cohort by quartiles of individual and neighborhood socioeconomic status^a

	Individual SES					Neighborhood SES				
	Q1	Q2	Q3	Q4	P Value	Q1	Q2	Q3	Q4	P Value
	(n=292)	(n=290)	(n=305)	(n=293)		(n=296)	(n=298)	(n=292)	(n=294)	
	No.(%)	No. (%)	No. (%)	No. (%)		No. (%)	No. (%)	No. (%)	No. (%)	
Demographics										
Education (higher education)	0 (0.0)	2 (0.7)	49 (16.1)	248 (84.9)	< .001	6 (2.0)	49 (16.5)	73 (25.0)	171 (58.4)	< .001
Occupation (white-collar)	0 (0.0)	0 (0.0)	44 (16.2)	224 (86.5)	< .001	21 (9.3)	90 (37.3)	125 (51.2)	181 (72.7)	< .001
Gender (female)	208 (71.2)	210 (72.7)	179 (58.7)	152 (52.1)	< .001	204 (68.9)	177 (59.4)	191 (65.4)	178 (60.5)	.058
ApoE (ε4)	52 (17.9)	49 (17.1)	60 (19.7)	53 (18.3)	.873	59 (20.1)	59 (19.9)	44 (15.2)	52 (17.9)	.386
Clinical variables										
Hypertension	165 (56.6)	157 (54.3)	159 (52.1)	142 (48.6)	.265	165 (55.7)	154 (51.7)	154 (52.7)	150 (51)	.670
Cholesterol	157 (54.1)	164 (57.1)	162 (53.1)	151 (52.2)	.662	155 (52.9)	182 (61.5)	158 (54.1)	141 (48.3)	.014
Diabetes	50 (17.1)	63 (21.8)	50 (16.4)	45 (15.4)	.186	51 (17.2)	58 (19.5)	51 (17.5)	48 (16.3)	.784
Stroke	20 (6.9)	12 (4.2)	16 (5.3)	17 (5.9)	.546	18 (6.1)	15 (5)	16 (5.5)	16 (5.5)	.952
Smoking	72 (24.7)	76 (26.3)	140 (45.9)	154 (52.7)	< .001	79 (26.7)	108 (36.2)	120 (41.1)	137 (46.6)	< .001
Depression	122 (41.8)	98 (33.9)	87 (28.5)	85 (29.1)	.002	105 (35.5)	104 (34.9)	98 (33.6)	86 (29.3)	.369
Auditory deficit	111 (38.0)	92 (31.8)	83 (27.2)	80 (27.4)	.014	117 (39.5)	98 (32.9)	71 (24.3)	82 (27.9)	< .001
Visual deficit	127 (43.5)	132 (45.7)	131 (43.0)	118 (40.4)	.645	121 (40.9)	145 (48.7)	114 (39)	129 (43.9)	.094
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P Value	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P Value
Demographics										
Age, y	75.4 (3.8)	75.4 (3.9)	74.8 (4.1)	74.1 (3.8)	< .001	75.4 (3.8)	74.7 (3.7)	74.6 (3.9)	75.0 (4.3)	.028
Cognition										
MMSE	27.4 (2.1)	28.1 (1.9)	28.9 (1.3)	29.2 (1.0)	< .001	27.8 (2.1)	28.4 (1.8)	28.5 (1.7)	28.9 (1.3)	< .001
FCSRT immediate free recall	20.3 (6.2)	21.4 (6.6)	23.5 (6.9)	25.6 (6.6)	< .001	20.8 (6.3)	22.5 (6.5)	23.2 (7.5)	24.4 (6.7)	< .001
FCSRT delayed free recall	8.2 (2.8)	8.2 (3.1)	9.5 (2.9)	10.2 (2.8)	< .001	8.2 (3.1)	9 (2.8)	9.2 (3.1)	9.7 (2.9)	< .001
Animals	15.8 (4.4)	16.9 (4.8)	19.2 (4.7)	20.5 (5.1)	< .001	16.3 (4.5)	18 (5)	18.6 (5.3)	19.6 (4.9)	< .001
Digit-Symbol	12.6 (5.2)	16.1 (5.9)	21.6 (6.8)	24.3 (6.3)	< .001	13.9 (5.8)	18.3 (7)	19.9 (8)	22.6 (6.7)	< .001
FAQ	1.0 (1.8)	0.9 (1.8)	0.4 (0.9)	0.4 (0.7)	< .001	0.9 (1.7)	0.6 (1.5)	0.7 (1.5)	0.4 (0.8)	.001
CDR sum of boxes	0.4 (0.6)	0.3 (0.6)	0.1 (0.3)	0.1 (0.2)	< .001	0.3 (0.5)	0.2 (0.5)	0.2 (0.5)	0.1 (0.3)	< .001
Neuroimaging										
Gray matter volume, cm ³	522 (63)	533 (56)	539 (54)	548 (55)	< .001	525 (62)	538 (57)	537 (54)	543 (57)	< .001
White matter volume, cm ³	469 (121)	464 (95)	476 (85)	485 (92)	< .001	464 (107)	476 (98)	472 (94)	484 (97)	< .001
Motor exam										
Up & Go test, sec	7.9 (2.1)	7.7 (2.1)	7.3 (1.8)	7.0 (2.0)	< .001	7.9 (2.1)	7.3 (2)	7.5 (2)	7.2 (2)	< .001
Taps right hand	56.5 (9.2)	57.8 (10.5)	61.4 (10.3)	63.0 (10.3)	< .001	57.6 (10.3)	59.9 (9.9)	59.5 (10.6)	61.8 (10.5)	< .001
Taps left hand	53.1 (8.4)	54.7 (10.0)	56.7 (9.8)	58.4 (9.7)	< .001	54.4 (9.5)	55.6 (9)	55.6 (9.4)	57.3 (9.7)	.003
Quality of life and lifestyle										
EQ5D	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	< .001	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	.007
Physical activity	2.2 (0.8)	2.2 (0.8)	2.2 (0.8)	2.3 (0.8)	.566	2.3 (0.8)	2.3 (0.8)	2.2 (0.8)	2.2 (0.8)	.156
Manual activity	1.5 (0.8)	1.5 (0.8)	1.4 (0.7)	1.4 (0.7)	.015	1.5 (0.8)	1.4 (0.7)	1.4 (0.7)	1.3 (0.7)	.019
Leisure activity	1.6 (0.7)	1.8 (0.6)	2.1 (0.7)	2.3 (0.6)	< .001	1.6 (0.7)	1.9 (0.7)	2 (0.7)	2.2 (0.6)	< .001
Creative activity	1.5 (0.7)	1.6 (0.8)	1.7 (0.8)	1.9 (0.8)	< .001	1.6 (0.8)	1.6 (0.7)	1.8 (0.8)	1.7 (0.8)	.055
Social activity	1.4(0.7)	1.4 (0.7)	1.6 (0.8)	1.8 (0.8)	< .001	1.4 (0.7)	1.6 (0.8)	1.6 (0.8)	1.6 (0.8)	.001
Reading	2.4 (0.8)	2.5 (0.6)	2.7 (0.6)	2.8 (0.4)	< .001	2.4 (0.7)	2.6 (0.6)	2.6 (0.6)	2.8 (0.5)	< .001
ICT use	1.2 (0.6)	1.4 (0.7)	1.9 (0.9)	2.4 (0.8)	< .001	1.3 (0.7)	1.7 (0.9)	1.8 (0.9)	2.1 (0.9)	< .001
Diet										
Fruit	2.8 (0.5)	2.7 (0.7)	2.7 (0.7)	2.7 (0.7)	.300	2.7 (0.6)	2.8 (0.5)	2.7 (0.7)	2.7 (0.8)	.209
Vegetables	2.2 (0.8)	2.3 (0.8)	2.3 (0.7)	2.3 (0.8)	.156	2.2 (0.8)	2.3 (0.8)	2.3 (0.7)	2.3 (0.8)	.411
Anthropometrics										
Weight, kg	69.1 (10.4)	69.3 (11.0)	70.8 (11.5)	71.8 (12.0)	.023	70.1 (10.9)	70.5 (10.7)	70 (11.8)	70.4 (11.8)	.758
Height, cm	157.0 (8.5)	158.8 (7.9)	162.0 (8.4)	163.5 (9.2)	< .001	157.4 (8.4)	160.9 (8.4)	160.1 (8.7)	163 (9.0)	< .001
BMI	28.0 (3.6)	27.4 (3.5)	26.9 (3.6)	26.8 (3.7)	< .001	28.2 (3.6)	27.2 (3.5)	27.2 (3.6)	26.4 (3.6)	< .001

Abbreviations: BMI, Body Mass Index; CDR, Clinical Dementia Rating; EQ5D, EuroQol-5D; FAQ, Functional Activities Questionnaire; FCSRT, Free and Cued Selective Reminding Test; ICT, Information and Communications Technology; MMSE, Mini Mental State Exam; Q, quartile.

^a Quartiles follow an ordinal distribution so that the upper quartile (Q4) corresponded to the best off, while the lower one (Q1) were referred to the worst off.

eTable 2. Baseline characteristics of males by quartiles of individual and neighborhood socioeconomic status^a

	Individual SES					Neighborhood SES				
	Q1	Q2	Q3	Q4	P Value	Q1	Q2	Q3	Q4	P Value
	(n=84)	(n=79)	(n=126)	(n=140)		(n=92)	(n=121)	(n=101)	(n=116)	
	No.(%)	No. (%)	No. (%)	No. (%)		No. (%)	No. (%)	No. (%)	No. (%)	
Demographics										
Education (higher education)	0 (0.0)	1 (1.3)	20 (15.9)	128 (91.4)	< .001	3 (3.3)	24 (20.0)	39 (38.6)	83 (71.6)	< .001
Occupation (white-collar)	0 (0.0)	0 (0.0)	38 (33.7)	118 (92.9)	< .001	3 (4.2)	32 (30.8)	40 (46.5)	81 (76.4)	< .001
Gender	-	-	-	-		-	-	-	-	
ApoE (ε4)	16 (19.3)	20 (25.6)	26 (20.6)	28 (20.1)	.747	21 (23.1)	29 (24.2)	12 (12.0)	28 (24.3)	.086
Clinical variables										
Hypertension	41 (48.8)	37 (46.8)	65 (51.6)	80 (57.1)	.444	39 (42.4)	65 (53.7)	57 (56.4)	62 (53.4)	.218
Cholesterol	43 (51.2)	33 (41.8)	64 (50.8)	74 (52.9)	.309	42 (45.6)	64 (53.0)	52 (51.5)	57 (49.1)	.179
Diabetes	24 (28.5)	17 (21.5)	29 (23.0)	26 (28.3)	.701	19 (20.6)	31 (25.6)	20 (19.8)	26 (22.4)	.265
Stroke	7 (8.3)	4 (5.1)	6 (4.8)	6 (4.3)	.662	6 (6.5)	5 (4.1)	8 (7.9)	4 (3.5)	.370
Smoking	57 (67.8)	56 (70.9)	88 (69.8)	101 (72.1)	.970	65 (70.7)	83 (68.6)	72 (71.3)	83 (71.6)	.553
Depression	19 (22.6)	14 (17.7)	16 (12.7)	27 (19.3)	.284	13 (14.1)	30 (24.8)	18 (17.8)	15 (12.9)	.078
Auditory deficit	32 (38.1)	31 (39.2)	42 (33.3)	39 (27.9)	.266	34 (37.0)	44 (36.4)	26 (25.7)	41 (35.3)	.281
Visual deficit	39 (46.4)	37 (46.8)	54 (42.9)	62 (44.3)	.934	39 (42.4)	56 (46.3)	48 (47.5)	50 (43.1)	.859
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P Value	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P Value
Demographics										
Age, y	75.3 (3.8)	76.2 (4.2)	74.9 (4.1)	74.1 (3.5)	.002	75.4 (4.0)	74.8 (3.8)	74.7 (3.9)	74.9 (4.1)	.526
Cognition										
MMSE	27.8 (1.8)	27.8 (2.1)	28.9 (1.3)	29.1 (1.1)	< .001	28.0 (1.9)	28.5 (1.6)	28.5 (1.6)	29.0 (1.2)	< .001
FCSRT immediate free recall	18.8 (6.1)	19.6 (7.0)	22.8 (6.6)	24.7 (6.6)	< .001	20.5 (7.0)	21.4 (6.5)	22.1 (7.4)	23.9 (6.7)	.007
FCSRT delayed free recall	7.9 (2.6)	7.4 (3.5)	9.3 (2.7)	9.7 (2.7)	< .001	8.1 (3.2)	8.6 (2.9)	8.8 (3.1)	9.6 (2.7)	.006
Animals	15.9 (4.5)	16.3 (4.7)	19.7 (4.7)	20.6 (5.3)	< .001	16.6 (5.3)	18.2 (4.8)	18.9 (5.3)	20.3 (5.1)	< .001
Digit-Symbol	13.1 (5.3)	15.8 (6.0)	22.3 (7.0)	25.1 (6.4)	< .001	14.5 (6.4)	19.2 (7.4)	21.8 (8.1)	24.4 (6.3)	< .001
FAQ	1.1 (1.4)	1.2 (1.7)	0.5 (0.8)	0.4 (0.8)	< .001	1.0 (1.5)	0.7 (1.2)	0.7 (1.3)	0.5 (0.8)	.181
CDR sum of boxes	0.4 (0.6)	0.4 (0.6)	0.1 (0.2)	0.1 (0.2)	< .001	0.3 (0.6)	0.2 (0.3)	0.2 (0.4)	0.1 (0.3)	.013
Neuroimaging										
Gray matter volume, cm ³	562 (50)	576 (42)	562 (60)	569 (53)	.284	561 (48)	569 (42)	562 (61)	571 (59)	.188
White matter volume, cm ³	500 (60)	512 (46)	512 (88)	514 (97)	.522	498 (51)	506 (46)	519 (114)	516 (89)	.239
Motor exam										
Up & Go test, sec	7.2 (2.2)	7.1 (1.9)	6.8 (1.7)	6.7 (2)	.081	7.1 (1.8)	6.7 (1.8)	7.1 (2.2)	6.7 (2)	.069
Taps right hand	58.0 (8.0)	58.7 (8.6)	64.4 (9.4)	63.7 (10)	< .001	59.8 (9.0)	62.2 (9.6)	61.4 (9.8)	63.5 (9.6)	.028
Taps left hand	54.7 (7.1)	55.8 (9.2)	59.6 (8.8)	60.0 (9.5)	< .001	56.3 (8.5)	58.0 (8.7)	57.8 (9.4)	59.8 (9.4)	.014
Quality of life and lifestyle										
EQ5D	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	1.0 (0.1)	.209	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	1 (0.1)	.005
Physical activity	2.1 (0.9)	2.2 (0.9)	2.2 (0.8)	2.3 (0.7)	.385	2.2 (0.9)	2.3 (0.8)	2.2 (0.8)	2.3 (0.8)	.624
Manual activity	1.2 (0.5)	1.2 (0.5)	1.2 (0.6)	1.3 (0.6)	.133	1.3 (0.6)	1.2 (0.5)	1.2 (0.6)	1.2 (0.5)	.935
Leisure activity	1.6 (0.6)	1.7 (0.6)	1.9 (0.6)	2.2 (0.6)	< .001	1.6 (0.6)	1.9 (0.6)	1.9 (0.6)	2.2 (0.6)	< .001
Creative activity	1.4 (0.7)	1.4 (0.7)	1.7 (0.8)	1.9 (0.8)	< .001	1.6 (0.8)	1.5 (0.7)	1.7 (0.8)	1.7 (0.8)	.270
Social activity	1.9 (0.8)	2.0 (0.7)	2.0 (0.6)	2.1 (0.6)	.060	2 (0.7)	2.0 (0.7)	1.9 (0.7)	2.1 (0.7)	.346
Reading	2.3 (0.8)	2.6 (0.6)	2.7 (0.5)	2.8 (0.4)	< .001	2.5 (0.7)	2.6 (0.6)	2.6 (0.6)	2.8 (0.4)	.003
ICT use	1.3 (0.6)	1.4 (0.8)	2.1 (0.9)	2.5 (0.8)	< .001	1.3 (0.7)	1.9 (0.9)	2.1 (0.9)	2.3 (0.9)	< .001
Diet										
Fruit	2.7 (0.6)	2.7 (0.7)	2.7 (0.6)	2.7 (0.7)	.948	2.6 (0.6)	2.8 (0.5)	2.6 (0.7)	2.7 (0.7)	.497
Vegetables	2.0 (0.8)	2.2 (0.8)	2.2 (0.7)	2.2 (0.7)	.281	2.1 (0.8)	2.1 (0.8)	2.1 (0.7)	2.2 (0.8)	.892
Anthropometrics										
Weight, kg	77.0 (9.8)	77.4 (9.9)	77.1 (11)	78.2 (11)	.861	77.2 (10.5)	76.5 (10.2)	77.7 (11.7)	78.4 (10)	.498
Height, cm	165.5 (6.6)	167.3 (6.4)	168.4 (6.5)	169.6 (7.5)	< .001	165.6 (5.8)	167.7 (7.0)	167.9 (7.7)	170.4 (6.5)	< .001
BMI	28.1 (3.3)	27.6 (3.0)	27.1 (3.1)	27.2 (3.7)	0.070	28.1 (3.2)	27.2 (3.3)	27.6 (3.6)	27.0 (3.2)	.063

Abbreviations: BMI, Body Mass Index; CDR, Clinical Dementia Rating; EQ5D, EuroQol-5D; FAQ, Functional Activities Questionnaire; FCSRT, Free and Cued Selective Reminding Test; ICT, Information and Communications Technology; MMSE, Mini Mental State Exam; Q, quartile.

^a Quartiles follow an ordinal distribution so that the upper quartile (Q4) corresponded to the best off, while the lower one (Q1) were referred to the worst off.

eTable 3. Baseline characteristics of females by quartiles of individual and neighborhood socioeconomic status^a

	Individual SES					Neighborhood SES				
	Q1	Q2	Q3	Q4	P Value	Q1	Q2	Q3	Q4	P Value
	(n=208)	(n=210)	(n=179)	(n=152)		(n=204)	(n=177)	(n=191)	(n=178)	
	No.(%)	No. (%)	No. (%)	No. (%)		No. (%)	No. (%)	No. (%)	No. (%)	
Demographics										
Education (higher education)	0 (0.0)	1 (0.5)	29 (16.2)	120 (78.9)	< .001	3 (1.5)	25 (14.1)	34 (17.8)	88 (49.7)	< .001
Occupation (white-collar)	0 (0.0)	0 (0.0)	6 (3.7)	106 (80.4)	< .001	4 (2.6)	16 (11.7)	29 (18.3)	63 (44.1)	< .001
Gender	-	-	-	-		-	-	-	-	
ApoE (ε4)	36 (17.3)	29 (13.9)	34 (19.0)	25 (16.7)	.583	38 (18.7)	30 (16.9)	32 (16.8)	24 (13.6)	.616
Clinical variables										
Hypertension	124 (59.6)	120 (57.1)	94 (52.5)	62 (40.8)	.003	126 (61.8)	89 (50.3)	97 (50.8)	88 (49.4)	.045
Cholesterol	114 (54.8)	131 (62.4)	98 (54.8)	77 (53.7)	.035	113 (53.4)	118 (66.6)	106 (55.5)	84 (47.2)	.021
Diabetes	26 (12.5)	46 (21.9)	21 (11.8)	19 (12.5)	.042	32 (15.7)	27 (15.3)	31 (16.2)	22 (12.4)	.814
Stroke	14 (6.8)	8 (3.8)	12 (6.7)	11 (7.2)	.841	13 (6.4)	10 (5.6)	8 (4.2)	13 (7.3)	.731
Smoking	15 (7.2)	20 (9.5)	52 (29.1)	53 (34.8)	< .001	14 (6.9)	25 (14.1)	48 (25.1)	54 (30.4)	< .001
Depression	103 (49.5)	84 (40.0)	71 (39.7)	58 (38.2)	.091	92 (45.1)	74 (41.8)	80 (41.9)	71 (39.9)	.775
Auditory deficit	79 (38.0)	61 (29.0)	41 (22.9)	41 (27.0)	.010	83 (40.7)	54 (30.5)	45 (23.6)	41 (23.0)	< .001
Visual deficit	88 (42.3)	95 (45.2)	77 (43.0)	56 (36.8)	.452	82 (40.2)	89 (50.3)	66 (34.6)	79 (44.4)	.019
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P Value	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P Value
Demographics										
Age, y	75.5 (3.7)	75.1 (3.8)	74.8 (4.1)	74.2 (4.1)	.002	75.4 (3.7)	74.7 (3.7)	74.5 (3.9)	75 (4.4)	.070
Cognition										
MMSE	27.3 (2.2)	28.2 (1.9)	28.9 (1.3)	29.3 (1.0)	< .001	27.7 (2.2)	28.4 (1.9)	28.5 (1.8)	28.9 (1.4)	< .001
FCSRT immediate free recall	20.9 (6.2)	22.1 (6.3)	24.1 (7.1)	26.4 (6.6)	< .001	21.0 (6.0)	23.2 (6.5)	23.8 (7.5)	24.7 (6.7)	< .001
FCSRT delayed free recall	8.4 (2.9)	8.5 (2.9)	9.6 (3.0)	10.6 (2.7)	< .001	8.2 (3.0)	9.3 (2.7)	9.4 (3.1)	9.8 (3.0)	< .001
Animals	15.8 (4.3)	17.1 (4.8)	18.9 (4.7)	20.4 (5.0)	< .001	16.2 (4.2)	17.9 (5.1)	18.4 (5.4)	19.1 (4.7)	< .001
Digit-Symbol	12.4 (5.2)	16.2 (5.8)	21.1 (6.6)	23.5 (6.1)	< .001	13.7 (5.6)	17.7 (6.7)	18.8 (7.7)	21.5 (6.7)	< .001
FAQ	0.9 (1.9)	0.8 (1.9)	0.4 (0.9)	0.3 (0.7)	< .001	0.8 (1.8)	0.6 (1.6)	0.6 (1.6)	0.3 (0.7)	.019
CDR sum of boxes	0.3 (0.6)	0.2 (0.6)	0.1 (0.3)	0.1 (0.3)	< .001	0.3 (0.5)	0.2 (0.6)	0.2 (0.6)	0.1 (0.3)	.003
Neuroimaging										
Gray matter volume, cm ³	508 (62)	519 (53)	524 (44)	531 (50)	< .001	510 (61)	518 (57)	525 (46)	523 (48)	< .001
White matter volume, cm ³	458 (135)	450 (101)	452 (74)	461 (80)	< .001	451 (120)	457 (115)	450 (73)	464 (96)	< .001
Motor exam										
Up & Go test, sec	8.2 (2.1)	7.9 (2.1)	7.6 (1.8)	7.4 (2.0)	.001	8.3 (2.1)	7.6 (1.9)	7.6 (1.9)	7.5 (2.0)	< .001
Taps right hand	55.9 (9.5)	57.4 (11.1)	59.2 (10.4)	62.4 (10.6)	< .001	56.6 (10.8)	58.3 (9.7)	58.5 (10.9)	60.6 (10.8)	< .001
Taps left hand	52.4 (8.7)	54.3 (10.2)	54.6 (8.4)	57.0 (9.7)	< .001	53.6 (9.8)	53.9 (8.9)	54.5 (9.3)	55.7 (9.6)	.032
Quality of life and lifestyle										
EQ5D	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	.001	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	.162
Physical activity	2.3 (0.8)	2.2 (0.8)	2.1 (0.9)	2.2 (0.8)	.485	2.3 (0.8)	2.3 (0.8)	2.2 (0.8)	2.1 (0.9)	.054
Manual activity	1.6 (0.9)	1.7 (0.8)	1.5 (0.8)	1.4 (0.7)	.016	1.7 (0.9)	1.6 (0.8)	1.6 (0.8)	1.4 (0.8)	.069
Leisure activity	1.6 (0.7)	1.8 (0.6)	2.2 (0.7)	2.4 (0.6)	< .001	1.6 (0.7)	1.9 (0.7)	2.0 (0.7)	2.2 (0.6)	< .001
Creative activity	1.6 (0.8)	1.6 (0.8)	1.7 (0.8)	1.8 (0.8)	.006	1.7 (0.8)	1.6 (0.7)	1.8 (0.9)	1.6 (0.8)	.165
Social activity	2.0 (0.8)	2.0 (0.8)	2.1 (0.7)	2.2 (0.6)	.036	2.0 (0.8)	2.1 (0.7)	2.0 (0.7)	2.2 (0.7)	.063
Reading	2.4 (0.7)	2.5 (0.7)	2.7 (0.6)	2.8 (0.4)	< .001	2.3 (0.8)	2.6 (0.6)	2.7 (0.6)	2.8 (0.5)	< .001
ICT use	1.2 (0.6)	1.3 (0.7)	1.8 (0.9)	2.3 (0.8)	< .001	1.3 (0.7)	1.5 (0.8)	1.7 (0.9)	1.9 (0.9)	< .001
Diet										
Fruit	2.8 (0.5)	2.7 (0.7)	2.7 (0.7)	2.7 (0.7)	.172	2.7 (0.6)	2.8 (0.6)	2.7 (0.6)	2.6 (0.8)	.157
Vegetables	2.3 (0.8)	2.3 (0.8)	2.4 (0.7)	2.4 (0.7)	.054	2.3 (0.8)	2.3 (0.8)	2.3 (0.7)	2.4 (0.7)	.245
Anthropometrics										
Weight, kg	65.9 (8.9)	66.2 (9.8)	66.4 (9.7)	65.8 (9.6)	.882	66.8 (9.4)	66.4 (9.1)	65.8 (9.5)	65.2 (9.9)	.272
Height, cm	153.6 (6.5)	155.6 (5.7)	157.5 (6.5)	157.9 (6.6)	< .001	153.8 (6.6)	156.3 (5.8)	156 (6.1)	158.1 (6.9)	< .001
BMI	28.0 (3.7)	27.3 (3.7)	26.8 (3.8)	26.4 (3.7)	< .001	28.3 (3.8)	27.2 (3.6)	27.0 (3.5)	26.1 (3.9)	< .001

Abbreviations: BMI, Body Mass Index; CDR, Clinical Dementia Rating; EQ5D, EuroQol-5D; FAQ, Functional Activities Questionnaire; FCSRT, Free and Cued Selective Reminding Test; ICT, Information and Communications Technology; MMSE, Mini Mental State Exam; Q, quartile.

^a Quartiles follow an ordinal distribution so that the upper quartile (Q4) corresponded to the best off, while the lower one (Q1) were referred to the worst off.

eFigure 1. Effect size of individual variables at baseline by Individual Socioeconomic Status and Neighborhood Socioeconomic Status upper and lower quartiles

Abbreviations: BMI, Body Mass Index; CDR, Clinical Dementia Rating; EQ5D, EuroQol-5D; FAQ, Functional Activities Questionnaire; FCSRT, Free and Cued Selective Reminding Test; ICT, Information and Communications Technology; ISES, individual socioeconomic status; MMSE, Mini Mental State Exam; NSES, neighborhood socioeconomic status.

This figure illustrates the magnitude of the effect in baseline individual variables according to the comparison of upper and lower quartiles of ISES and NSES. The red points represent the effect size associated with ISES, while blue points are referred to NSES. The variables are ordered from the highest to the lowest mean effect size. The Digit-Symbol test shows the greatest size effect and Depression the smallest effect. Overall, a consistent trend can be observed across the variables whereby the differences for ISES are greater than for NSES (the red dot is predominately on the right of the blue dot). The exceptions are some biological variables such as volumetry of Gray and White matter, Body Mass Index and Auditory Deficits in which effect sizes are greater for NSES.