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ABSTRACT

Unequal Expression: Social Position, APOE Genotype and Risk of Dementia

The influence of genetic risk on dementia can be shaped by social environments. Following older adults without dementia at baseline for 12 years in two large cohorts—Health and Retirement Study (HRS) and English Longitudinal Study of Ageing (ELSA), we examine how APOE alleles interact with social adversity to determine dementia risk. A social adversity index is constructed based on five domains of social determinants of health outlined in the Healthy People 2030: education access, economic stability, healthcare quality, neighborhood environment, and social context. Participants are classified as having low (APOE-ε2), intermediate (APOE-ε3/ε3), or high (APOE-ε4) genetic risk of dementia. Dementia is ascertained via clinical diagnosis, cognitive testing, or validated caregiver report. Genetic effects are most pronounced among individuals with social advantage. In contrast, those experiencing high social adversity have elevated dementia risk regardless of genotype. Notably, individuals with high genetic risk but social advantage have lower dementia risks than those with low genetic risk but high social adversity. Addressing social adversity may reduce dementia risk across genotypes and enhance equity in dementia prevention.

JEL Classification: I14, I24, I10, J14, J15, H75

Keywords: social adversity, social advantage, genetic risk, genotype, dementia, United States, United Kingdom

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1. Introduction

Dementia is a growing global public health challenge.(1) In response, prevention science and risk prediction strategies have increasingly focused on identifying biomedical and genetic risk factors to inform early intervention. Among genetic markers, the apolipoprotein E (APOE) gene stands out as the most robust predictor of late-onset Alzheimer's disease and vascular dementia risk.(2) These insights have led to the increasing use of polygenic risk scores, biomarker testing, and genotype-stratified interventions aimed at identifying individuals at high risk.(3,4) However, this precision approach often overlooks the profound influence of social determinants of health, which shape cognitive aging through lifelong exposure to structural disadvantage.(5) Social adversity, defined as cumulative disadvantage across domains such as education, income, healthcare access, neighborhood, and social environment,(6) has emerged as a critical driver of dementia risk.(7) Yet, prevention strategies and risk prediction models frequently incorporate social factors merely as covariates or isolated determinants of disease, rather than recognizing them as broader contextual forces that can fundamentally shape how individual-level risks, such as genetic predisposition, are expressed.(8)

This disconnect raises an urgent question: how does social adversity interact with genetic predisposition to shape dementia outcomes? Understanding this interaction is not only scientifically relevant but also essential for designing equitable prevention strategies that recognize the dual impact of biology and environment,(9) and for ensuring that genetic risk information is interpreted appropriately across social strata.(10) Without this understanding, we risk implementing policies that exacerbate inequalities or misclassify risk in socially disadvantaged populations.

Two theoretical models offer competing predictions about how genes and environments interact to influence dementia risk. The social trigger model (Fig 1A) posits that genetic effects are magnified under high social adversity: stressful environments trigger the phenotypic expression of risky genes and amplify the benefits of protective variants.(11) In this model, genetic risk is masked in advantaged settings and revealed under strain.(12) By contrast, the social distinction model (Fig 1B) suggests that genetic effects are more pronounced among individuals with social advantage.(13) Here, supportive environments provide the physiological and psychological

conditions that allow genes (whether protective or harmful) to fully manifest, while adversity exerts such a strong influence on health that it overshadows genetic variation.(14)

Despite the importance of these competing models, few empirical studies have directly compared them in relation to dementia risk, particularly using multidimensional measures of social adversity and large-scale population data. Moreover, it remains unclear whether APOE-associated dementia risk is shaped or suppressed by the social environments in which individuals age.(15)

To address this gap, we used harmonized data from two nationally representative studies of older adults with similar genetic ancestry and measurement protocols: the Health and Retirement Study (HRS) in the United States and the English Longitudinal Study of Ageing (ELSA). These studies offer rich data on APOE genotypes, social determinants of health, and longitudinal cognitive outcomes, enabling us with the unique opportunity to test gene-environment interactions at scale.

We hypothesized that data would support the social distinction model, for two reasons. First, previous studies of dementia risk factors that have found that as social adversity increases, so does the number of dementia risk factors.(16) Second, the health burden combined with the psychological stressors of living under social adversity can be substantial, negatively affecting epigenetic aging(17) and thus likely exceeding the protective or harmful effect of the APOE- ε2 and ε4 alleles, respectively. Conversely, among those living with low social adversity, psychological and health factors will be optimal leading to reduced impact on epigenetic aging. Therefore, the APOE alleles will have more room for their phenotypical expression, making evident its harmful or beneficial impact on dementia risk.

Accordingly, we tested two hypotheses: a) The impact of APOE alleles on dementia risk will be more pronounced among individuals with low social adversity as opposed to those exposed to high social adversity; and b) Higher social adversity will be associated with elevated dementia risk, regardless of APOE genotype.

2. Study Design, Data and Measures

2.1 Study design and population

Study report follows the STROBE statement for cohort studies (Supporting information S1). This was a secondary data analysis of two prospective nationally representative sister cohort studies: the Health and Retirement Study (HRS)(18) and the English Longitudinal Study of Ageing (ELSA).(19) HRS is a nationally representative study of more than 37,000 individuals 51 years or older in the U.S., that measures several economic, psychosocial, and health factors of aging. In 2006, the study added genetic information. HRS has followed people for 15 waves every two years from 1992-93 to 2020-22. For this study, people were followed from the first HRS wave were genetic and SDH information was available, 2006 (wave 8) to 2018 (wave 14). ELSA is a nationally representative study with more than 18,000 individuals in England. ELSA is the sister study of HRS applying almost the same measurement procedures but in a population 50 years or older. The study has followed people for 11 waves every two years from 2002-03 to 2018-20. ELSA added genetic information in 2004 – 2005. For this study, people were followed from the first ELSA wave were genetic and SDH information was available, 2010 (wave 5) to 2018 (wave 8).

2.2 Inclusion criteria and selection of participants

For this analysis, we included all the participants ≥ 55 years, free of dementia at baseline, with available genetic (APOE) and SDH information at baseline, and at least two consecutive waves of the outcome (dementia). People with one or more wave gaps in dementia were excluded to avoid uncertainty about when dementia started.

Supporting information Figure S1 describes the participants' study selection. At baseline, 7,954 and 5,531 participants had genetic and complete SDH information in HRS and ELSA, respectively. Of the HRS participants, 424 were excluded for not having cognitive or dementia information, 1,502 were less than 55 years old, 164 had dementia at baseline, and 67 had no follow-up. Of the ELSA participants, 15 were excluded for not having cognitive or dementia information, 106 were less than 55 years old, 124 had dementia at baseline, and 48 had no follow-up. The final pooled sample for analysis was 9,849 participants (HRS= 5,797, ELSA= 4,052) and followed up for up to 12 years (HRS= 12 years, ELSA= 8 years).

2.3 Genetic information and APOE risk classification

Genetic data management and information by cohort study is described in detail in the Supporting information S2 section. Genetic variants used for identifying APOE allele were rs7412 and rs429358. Individuals of both studies were classified according to their APOE risk profile as low risk (APOE-ε2ε2 or ε2ε3 carriers), intermediate risk (APOE-ε3ε3 carriers), or high risk (APOE-ε2ε4, ε3ε4, or ε4ε4 carriers).

For sensitivity analyses, a polygenic risk score (PGS) for AD dementia that did not include the APOE allele was used. Participants were classified according to their PGS for AD dementia score by cohort and ancestry in three groups: low risk (< 25th quartile score), intermediate risk (25th - 75th quartile score), and high risk (> 75th quartile score) of dementia.

2.4 Social adversity assessment

To create an index that reflect a theoretical explanation of cumulative health inequalities and considers the comprehensive definition of social adversity, we created an indicator using SDH measured in the same fashion in both cohort studies. These SDH reflected the five SDH areas defined by *Healthy People 2030 framework*:(20) education access, economic stability, neighborhood environment, healthcare access and quality, and social context. Specific SDH measured are described in the Supporting information S2 section.

Social adversity was measured as the number of unfavorable social determinants (number of SDH in the lowest level or lower quartile). Unfavorable SDH considered were less than upper secondary education, low family income (<25th quartile income), high neighborhood physical disorder (<25th quartile score), low neighborhood social cohesion (<25th quartile score), having experienced healthcare discrimination, not having some private healthcare insurance, low social support (<25th quartile score), and having experienced two or more different types of discrimination. People were categorized into four levels of social adversity according to the number of unfavorable SDH presented: none or one unfavorable SDH (low social adversity), two, three, or four or more unfavorable SDH (high social adversity).

For sensitivity analysis, a second measure reflecting social advantage was created, counting the number of favorable social conditions (number of SDH in the highest level or highest quartile). Favorable SDH considered were tertiary education, high family income (>75th quartile income), low neighborhood physical disorder (>75th quartile score), high neighborhood social cohesion (>75th quartile score), no experiences of healthcare discrimination, having some private healthcare insurance, high mean social support (>75th quartile score), and no experiences of any type of discrimination. People were categorized into four levels of social advantage according to the number of favorable SDH presented: none or one favorable SDH (low social advantage), two, three, or four or more favorable SDH (high social advantage).

2.5 Outcome variable – dementia

The main outcome was dementia incidence, and it was identified in the same fashion in both cohort studies. Dementia was ascertained if the participant fulfilled one or more of the three criteria: a) self-reported diagnosis of AD or dementia by a physician; or b) the coexistence of cognitive and functional impairment, defined following a previously validated method in HRS and ELSA samples based on the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV),(21) as having at least two cognitive domain scores of 1.5 S.D. lower than the mean of the population stratified by education level for those cognitive domains. Cognitive domains measured were executive functions (HRS: backward counting, serial 7s; ELSA: verbal fluency, numeracy score), orientation (HRS and ELSA: date naming tasks), and memory (HRS and ELSA: delayed word recall, immediate word recall). Functional impairment was defined as having difficulties performing one or more activities of daily living (bathing, eating, dressing, getting into and out of bed, and walking across a room); or c) in the case of people unable to respond, a proxy informant diagnosis using the 16-item interview of cognitive functioning scale (IQCODE) was used.(22) IQCODE contrasts the present functional and cognitive performance with the past two years' performance. A threshold of ≥ 3.38 has shown 0.82 sensitivity and 0.84 specificity to identify dementia, and no differences in performance between HRS and ELSA samples.(23)

2.6 Covariates

Covariates included in all the models were age, gender, and race or ethnicity. These variables were selected as those that predicted the exposure and the outcome and are not mediators in estimating the total effect.

Considering that a potential mediator of the association between social adversity and dementia risk is the number of dementia risk factors,(24) we measured for sensitivity analysis the presence (Yes/No) of eight evidence-based potentially modifiable risk factors of dementia:(7) hypertension, diabetes, obesity, smoking, high-frequency drinking (drinking more than 5 days a week), physical inactivity (participating <1 time per week in moderate or vigorous physical activity), self-reported hearing problems, and depression (CES-D score >2 points).

3. Statistical Analysis

3.1 Empirical strategy

For the analysis, we pooled participants from both studies to power the gene-environment interaction analyses that require a larger sample size. We used the Moore, Jacobson, & Fingerling power and sample size calculations formula for testing gene-environment interactions,(25) with power calculations based on a likelihood ratio test framework implemented in an open-source R package 'genpwr' (https://cran.r-project.org/web/packages/genpwr/index.html). Considering APOE is a dominant gene with prevalence of 12% for APOE-ε2 and 26% for ε4, and accounting that 12% of our population is exposed to high social vulnerability (≥ 4 unfavorable SDH), we estimated that a pooled sample size of 9,500 participants will have 86.0% and 94.2% power to detect APOE-ε2 and ε4-social vulnerability interactions of ratio 1.25 (Cohen's d effect size= 0.123, small effect size) in a 5.0 x 10^{-5} significance level, respectively.

In the pooled sample, we described the baseline characteristics of included participants according to their APOE risk profile (low, intermediate, or high risk). Differences among groups in categorical and continuous variables were calculated using the Chi-Square test (X^2) and ANOVA test, respectively. The same procedure was conducted to compare cohorts' baseline characteristics and included and excluded participants' characteristics.

For all the main analyses, we used generalized Cox regression models considering a 95% confidence interval (CI) and two-sided p-value <0.05 for estimating the Hazard Ratio (HR) of dementia. We used random effect models (I^2) to estimate the overall effect in the pooled sample,(26) adjusting for age, sex, race, and country (the U.S. or England). Survival time was defined as the month of the interview when dementia was identified in the HRS or ELSA. Participants were censored if they were lost to follow-up, if they died without dementia before the end of the study, or if they completed the study with no dementia. All the model's hazard proportionality assumptions were assessed using the Schoenfeld residuals test.

To test our first hypothesis, we assessed the interaction effect between participants' APOE risk profile, and social adversity levels on dementia HR. Then, to examine if the impact of APOE alleles will be evident for those who are at low social adversity (≤ 1 unfavorable SDH) as opposed to those who are at high social adversity (≥ 4 unfavorable SDH), we estimated the HR of dementia by APOE risk profile in every social adversity level, using people at intermediate APOE risk (APOE-ε3ε3) exposed to the lowest level of social adversity (≤ 1 unfavorable SDH) as the reference value.

To test our second hypothesis, we estimated the HR of dementia by social adversity level in the complete pooled sample and by APOE risk profile, using the lowest level of social adversity (≤ 1 unfavorable SDH) as reference value. A p-value for assessing linear trends in every model was estimated. All these analyses were also performed by cohort (HRS and ELSA).

Six sensitivity analyses were conducted to assess the robustness of the findings and are described in detail in the Supporting information SI.1 section. The analyses evaluated if the results remind consistent using social advantage as exposure, if the effect is maintained using a polygenic risk score excluding APOE allele, if potential reverse causality influenced results by excluding people with MCI at baseline, using a unique outcome assessment method based on cognitive scores, adjusting by eight evidence-based dementia risk factors, and assessing potential selection bias by calculating the inverse probability of being selected in the study.

Finally, subgroup analyses by sex (female and male), race (Black and White people), and specific social determinants were conducted to explore group differences and to identify which social determinants showed the strongest interaction with APOE genotype in terms of increasing dementia risk. All the analyses were conducted using Python 3.8.5 'pandas' package (https://pandas.pydata.org/) and R version 4.3.3. packages 'survminer' (https://cran.r-project.org/web/packages/survminer/index.html), 'survival' (https://cran.r-project.org/web/packages/survival/index.html), and 'coxme' (https://cran.r-project.org/web/packages/coxme/index.html).

3.2 Data availability

Phenotypic and survey data from the Health and Retirement Study (HRS) are publicly available via https://hrs.isr.umich.edu/data-products. Phenotypic data from the English Longitudinal Study of Ageing (ELSA) are available via https://ukdataservice.ac.uk. Access to genetic data from both HRS and ELSA is subject to legal and ethical restrictions due to the sensitive nature of genetic information. HRS genetic data can be requested via https://hrs.isr.umich.edu/data-products/genetic-data, and ELSA genetic data can be requested via https://www.elsa-project.ac.uk/genetic-data-access.

3.3 Ethics statement

This study is a secondary analysis of publicly available, de-identified data from both cohort studies. The ELSA study received ethical approval from the London Multi-Centre Research Ethics Committee, the National Hospital for Neurology and Neurosurgery & Institute of Neurology Joint Research Ethics Committee, and the South Central – Berkshire Research Ethics Committee. The HRS study was approved by the University of Michigan Institutional Review Board. All participants in both studies provided informed consent, and all data used in this analysis were anonymized prior to access. No additional ethical approval was required for this secondary analysis.

4. Results

Baseline characteristics and differences by APOE allele profile and cohort are described in Table 1 and Supporting information S1 Table, respectively.

The APOE allele distribution in the population was 12.8% APOE-ε2 (ELSA=13.5%, HRS=12.2%), 60.6% APOE-ε3ε3 (ELSA=59.5%, HRS=61.4%), and 26.6% APOE-ε4 (ELSA=27.0%, HRS=26.4%), with no significant differences between samples (P-value=0.077). People who are APOE-ε4 carriers were younger (mean age APOE-ε2=68.64, APOE-ε3ε3=68.68, APOE-ε4=67.82, P-value<0.001), a greater number of non-Hispanic Black people were APOE-ε4 carriers (APOE-ε2=8.3%, APOE-ε3ε3=6.6%, APOE-ε4=10.2%, P-value<0.001), Hispanic people were APOE-ε3ε3 carriers more often (APOE-ε2=4.2%, APOE-ε3ε3=9.0%, APOE-ε4=6.8%, P-value<0.001), and a greater proportion of APOE-ε2 carriers referred high social support (APOE-ε2=29.3%, APOE-ε3ε3=25,7%, APOE-ε4=23.9%, P-value=0.009). No other differences were found among APOE allele groups at baseline. All these variables were included as covariates in the main and sensitivity analyses models.

4.1 Social adversity-by-APOE allele risk interactions

As predicted by the first hypothesis, the impact of APOE alleles was more evident in people privileged to live with low social adversity as opposed to those exposed to greater social adversity for whom the impact of the APOE alleles had no significant impact (as suggested by the social distinction model); we found the interaction effect between social adversity and APOE allele profile was significant (P for social disadvantage x APOE interaction=0.001) (Fig 1C).

In the low social adversity level (≤ 1 unfavorable SDH), people at low (ε2) and high (ε4) genetic risk profiles presented the lowest (APOE-ε2 HR=0.67, 95%CI=0.48 – 0.93) and the highest (APOE-ε4 HR=1.68, 95%CI=1.37 – 2.06) risk of dementia, respectively, compared to people at intermediate genetic risk (ε3ε3) exposed to ≤ 1 unfavorable SDH (Fig 1C, Table 2). In contrast, as social adversity levels increased, dementia risk was greater and similar among APOE allele profiles, compared to people at intermediate genetic risk (ε3ε3) exposed to ≤ 1 unfavorable SDH (≥ 4 unfavorable SDH, APOE-ε2 HR=3.26, 95%CI=2.06 – 5.16; APOE-ε3ε3 HR=3.12, 95%CI=2.47 – 3.95; APOE-ε4 HR=3.21, 95%CI=2.34 – 4.41, Random effect (I^2) =0.0%) (Fig 1C, Table 2).

4.2 Social adversity and the risk of dementia

In support of the second hypothesis, we found that greater social adversity was associated with a significantly higher risk of dementia (P for linear trend<0.001) (Fig 2A-2C). In the linear association, for every increment in social adversity levels, the risk of dementia increased 0.42 times (HR=1.42, 95%CI=1.28 – 1.56, I^2=0.0%).

Regarding social adversity effect by APOE alleles groups, we found that greater social adversity was related to a higher risk of dementia in all the APOE allele profiles (Fig 3A-3C and Table 3). To illustrate the impact of social adversity on APOE allele effect, compared to people at intermediate genetic risk (ε3ε3) exposed to ≤ 1 unfavorable SDH, people at high genetic risk (ε4) in the lowest level of social adversity presented a lower risk of dementia than people at low genetic risk (ε2) in the highest level of social adversity (APOE-ε4 and low social adversity HR=1.68, 95%CI=1.37 – 2.06; APOE-ε2 and high social adversity HR=3.26, 95%CI=2.06 – 5.16) (Fig 1C, Table 2).

4.3 Social adversity, APOE allele, and dementia risk by country

In the assessment of results by study country (the U.S. and England), a trend supporting hypothesis one was observed, suggesting that the pooled sample with the larger power is needed to detect the gene-environment interaction effect. Differences in dementia risk were found between APOE allele profiles in the lowest social adversity level, although these were non-significant (Table 2). Consistent with the hypothesis, as social adversity levels increased, the risk of dementia was similar for individuals with intermediate and high genetic risk in the ELSA and HRS samples (Table 2).

In both samples, hypothesis two was supported, with consistent patterns across both cohorts indicating that greater social adversity increased the risk of dementia in all the APOE allele groups (Fig 2B and 2C, Table 3).

4.4 Sensitivity analyses

First, to evaluate if the results remind consistent if we use social advantage level as exposure, we created an indicator of social advantage counting the number of favorable social determinants (e.g., high income, high neighborhood social cohesion, and high social support). Using this

definition, the results follow the same pattern as the main analysis, where at low social advantage (≤ 1 favorable SDH), no statistically significant differences between APOE alleles were observed (APOE-ε2 HR=0.68, 95%CI=0.35 – 1.34; APOE-ε4 HR=1.34, 95%CI=0.90 – 2.01), while at the greater level of social advantage (≥ 4 favorable SDH), the differences between APOE-ε2 and APOE-ε4 were statistically significant in the expected direction (APOE-ε2 HR=0.29, 95%CI=0.19 – 0.43; APOE-ε3ε3 HR=0.47, 95%CI=0.35 – 0.62; APOE-ε4 HR= 0.75, 95%CI= 0.55 – 1.01) (S2 Figure S2 and S2 Table).

Second, to determine if the social adversity effect is maintained using a different definition of the dementia genetic risk profile, individuals were categorized into three genetic risk profiles based on quartiles of AD dementia polygenic risk scores that do not include APOE alleles: low (< 25^{th} quartile score), intermediate (25^{th} - 75^{th} quartile score), and high (> 75^{th} quartile score) polygenic risk profiles. Results indicated that the impact of social adversity on increasing dementia risk remained similar across different polygenic risk profiles, as observed in the main analyses (S3 Table).

Third, to address the possibility of reverse causality, we excluded people with mild cognitive impairment (n = 494) or dementia at baseline. The results obtained were similar to the main analyses, confirming a low possibility of reverse causality in our findings (S4 Table).

Fourth, to assess whether the results are influenced by the outcome assessment method, we included cases of dementia based solely on cognitive scores and functional limitations, finding that the results followed the same direction that those obtained in the main analyses (S5 Table).

Fifth, to examine if results remain consistent after considering dementia risk factor burden, a mediator in the causal path between social adversity and dementia risk, we conducted the same analyses but additionally adjusting by eight evidence-based potentially modifiable risk factors of dementia.(7) As expected, the association effect' sizes were slightly reduced, but all the analyses presented the same direction and statistically significant association as the main analysis (S6 Table).

Finally, to address potential selection bias due to differences between included and excluded individuals, we calculated the inverse probability of being selected by study cohort.(27) All analyses were weighted by the inverse probability of being selected for the study. Observed results from the weighted analysis did not differ from those obtained in the primary analyses, confirming a low chance of selection bias in our findings (S7 and S8 Tables).

4.5 Sub-group analyses

Subgroup analysis by sex showed that, in both males and females, the same pattern of APOE allele impact was observed: the effect was more evident among individuals living with low social adversity, whereas among those exposed to greater social adversity, the influence of the APOE allele was less pronounced (S9.a Table). However, the impact of social adversity on APOE genotype subgroups was more evident in women. We also observed that the effect of social adversity on male APOE-ε2 carriers was less pronounced than in female carriers, whereas the opposite pattern was found for APOE-ε4, with a stronger effect among female carriers compared to male carriers (S9.b Table).

Regarding racial differences (Black and White individuals), the same effect was observed: people at high social disadvantage presented the greatest risk of dementia, regardless of APOE allele (S10.a Table). Among White participants, APOE-ε2 carriers at social advantage presented a lower risk of dementia, and APOE-ε4 carriers at social advantage had a greater risk of dementia than APOE-ε3ε3 carriers at social advantage (S10.b Table). In contrast, among Black participants, APOE-ε2 carriers at social advantage did not present a lower risk of dementia, and APOE-ε4 carriers at social advantage showed no difference in dementia risk compared to APOE-ε3ε3 carriers at social advantage (S10.b Table).

4.6 Social determinants and APOE allele groups

Regarding individual social determinants, having a lower education level and lower family income presented the strongest interactions and were associated with a greater risk of dementia, regardless of APOE allele group (S11.a Table). Interestingly, among APOE-ε4 carriers, only having less than upper secondary education was associated with greater dementia risk, whereas

dementia risk remained elevated across all income levels (intermediate and low) when compared to those with high family income (S11.a Table).

In terms of healthcare-related factors, lower access to and quality of healthcare were associated with increased dementia risk among APOE-ε3ε3 and APOE-ε4 carriers (S11.b Table). Meanwhile, lower perceived social support and higher levels of neighborhood physical disorder were linked to greater dementia risk among APOE-ε2 and APOE-ε3ε3 carriers (S11.b and 11.c Tables). Finally, lower neighborhood social cohesion was associated with increased dementia risk, but only among APOE-ε3ε3 carriers (S11.c Table).

5. Discussion

In this study, we addressed a central question in the gene-environment debate: how does social position interact with genetic predisposition to shape dementia risk? Our findings support the social distinction model, which posits that genetic effects are more pronounced in socially advantaged contexts. Specifically, we found that the influence of APOE alleles on dementia risk was most evident among individuals with low social adversity, while among those experiencing high social adversity, APOE genotype had minimal impact. These findings suggest that social context can either amplify or attenuate the phenotypic expression of genetic risk for cognitive decline associated with APOE.

Consistent with our second hypothesis, we found that greater cumulative social adversity was associated with higher dementia risk, regardless of APOE status. Strikingly, individuals with high genetic risk (APOE-ε4) but low social adversity had a lower risk of dementia than those with low genetic risk (APOE-ε2) but high social adversity. These results highlight the dominant role of social conditions in modulating biological vulnerability, a finding with profound implications for precision medicine and public health equity.

Our results build on prior work showing that socioeconomic deprivation is associated with increased risk of dementia and poorer brain functioning.(28–30) Unlike earlier studies, we demonstrate that all APOE allele variants, as well as polygenic risk for Alzheimer's disease, interact with cumulative social adversity in a manner consistent with the social distinction model.

This suggests that the social gradient, whether measured by adversity or advantage, modulates the influence of genetic risk on dementia outcomes. These findings raise important considerations for gene discovery efforts, such as genome-wide association studies (GWAS) and polygenic risk score (PRS) development: the expression and statistical detectability of genetic associations with cognitive aging may depend on the social context in which individuals age. Without accounting for social conditions as potential moderators, studies may overlook candidate genes or misestimate their significance across socially diverse populations.(31)

In the same line, our findings underscore the need for future research to develop new methods for evaluating the accuracy and clinical utility of genetic risk models for dementia; approaches that move beyond treating social determinants as covariates or fixed risk factors and instead conceptualize them as dynamic modulators of gene expression.

Taken together, these insights point to the importance of pursuing multi-level, gene-environment approaches to dementia prevention. Targeting either APOE-related pathways or social environments in isolation may be insufficient to reduce dementia risk, particularly among socially disadvantaged populations.(9)

Among individuals exposed to high social adversity, dementia risk was not only similar across APOE genotypes but also higher than in any other genetic or social adversity group. This finding underscore how multidimensional social adversity can outweigh both protective and risky genetic profiles in determining cognitive health outcomes.(14) These results highlight the importance of developing upstream social and public health policies aimed at reducing social adversity as a strategy for dementia prevention that can benefit individuals regardless of their genetic risk. Furthermore, they support the integration of comprehensive measures of social adversity into precision medicine frameworks and dementia risk prediction models.

Nevertheless, we acknowledge that some individual SDH may interact with genetic risk in ways more consistent with the social trigger model,(12,32) and that interactions may vary across specific cognitive domains, other genetic variants, or life-course exposures.(33) Our findings also suggest that these interactions may differ across social identities, with variations by sex and

race indicating that social context may not only amplify or buffer genetic risk, but do so in ways shaped by structural inequality. Future research should explore these intersectional effects more explicitly, integrating sex, race, and other axes of identity into gene-environment models to better capture how societal structures shape dementia risk. Continued research is needed to examine these complexities and better characterize how social environments shape gene-related dementia risk.

One plausible pathway by which social adversity may influence dementia is through modifiable lifestyles and chronic disease risk factors.(34) The burden of potentially modifiable dementia risk factors is significantly greater in populations who live in poorer regions and low- and middle-income countries.(35) Yet, studies suggest that the association between socioeconomic status and dementia risk is mediated only up to 25% by unhealthy lifestyles.(36) In our analysis, controlling for eight evidence-based risk factors of dementia attenuated effect sizes, but results remained consistent, suggesting that other relevant factors related to chronic psychological stress may also contribute to the association between social adversity and dementia risk. This likely includes situations frequently faced by older people at social adversity, such as food insecurity,(37) exposure to environmental contaminants,(38) traumatic experiences,(39) age discrimination,(40) and lack of appropriate healthcare access.(41) Future moderator and mediator analyses are vital to informing experimental studies testing structural interventions for dementia risk reduction.

In our study, social adversity displayed a similar pattern in HRS and ELSA of impact on dementia risk in both samples, reinforcing its association with brain health in both social contexts. This is impressive given the many differences between the U.S. and England, such as the amounts of income inequality, and neighborhood segregation, as well as the type of healthcare systems.(42) Nonetheless, we acknowledge that the American and British populations share many cultural and genetic ancestry features that can favor the similarity of results between samples. Results demonstrating that social factors may be more relevant than genetic ancestry on dementia risk have also been found in Latin American populations,(43) reinforcing the validity of our results. Despite this, we encourage the replication of these findings in additional places, particularly low—and middle-income countries.

A limitation of our study is that the two final datasets could have had larger racial and ethnic diversity. In future research studying the gene-environment models, examining the additional contribution of race, ethnicity, and exposure to SDH to the patterns described will be relevant. Another limitation is that SDH were measured at a single point in time. However, considering that the U.S. and the England have faced the most significant decrease in social mobility in the last 50 years,(44) it is likely that these variables stayed consistent for most of the participants. Finally, while this study identifies statistically robust gene-environment interactions, it does not establish a causal relationship between social adversity and the modulation of APOE-related dementia risk. Social adversity was not exogenously assigned, and residual confounding cannot be ruled out. Our findings should be interpreted as descriptive of differential risk patterns that are nonetheless critical for informing future research, prevention strategies, and equity-oriented risk prediction.

Our study has several strengths. We used two of the largest and most rigorously harmonized longitudinal cohorts of aging, HRS and ELSA, which enabled prospective analysis of dementia across diverse national settings. We applied a comprehensive, multidimensional operationalization of social determinants of health (SDH) based on the Healthy People 2030 framework,(20) capturing economic, educational, healthcare, social, and environmental dimensions. Unlike most prior studies, we included all APOE genotypes, allowing for nuanced analyses of gene–environment interactions. Dementia diagnoses were harmonized using validated algorithms across cohorts, enhancing comparability. Finally, we conducted six complementary sensitivity analyses, reinforcing the internal validity and robustness of our findings.

Beyond these methodological strengths, this study makes a unique contribution by being the first to robustly test the social distinction model of gene–environment interaction in the context of dementia. Unlike prior research that has focused on additive effects of genes and environment, our findings demonstrate how social advantage and disadvantage modify the expression of genetic risk, revealing that genetic risk may be less detectable, and potentially less actionable, in contexts of structural adversity. These insights help explain disparities in dementia incidence

across social groups and suggest that the predictive value of genetic information is not universal, but conditional on societal context. This novel approach deepens our understanding of how macro-level factors shape biological vulnerability and offers a compelling case for incorporating SDH into precision brain health efforts.

In conclusion, our findings demonstrate that the influence of APOE genotype on dementia risk is shaped by social position, consistent with a social-distinction model. Genetic effects were amplified under social advantage and diminished under adversity. These results call for an integrated approach to dementia prevention that accounts for both biological and social risk, and that prioritizes structural strategies to reduce adversity, particularly among vulnerable groups. Equitable public health and precision medicine efforts will require a dual lens on genetic and social risk to maximize brain health in aging populations.

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Supporting Information

S1. STROBE Statement—Checklist of items to be included in reports of cohort studies.

S2. Social determinants of health and genetic data measurement.

S1 Table. Descriptive characteristics of ELSA and HRS sample included at baseline.

S2 Table. Analysis of social advantage on the risk of dementia according to APOE allele risk profile.

S3 Table. Analysis of social adversity on the risk of dementia according to polygenic risk score of AD profile.

S4 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile excluding people with mild cognitive impairment.

S5 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile in dementia cases identified using cognitive and functional impairment only.

S6 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile adjusting by the number of dementia risk factors.

S7 Table. Descriptive statistics of ELSA and HRS sample included and excluded based on complete social determinants of health information available at baseline.

S8 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile weighting by the inverse probability of being selected in the study.

S9 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile by sex.

S10 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile by race.

S11 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile by individual social determinants.

S1 Figure. Participant's study selection for HRS and ELSA populations.

S2 Figure. Social advantage Interacts with APOE Allele to Determine Risk of Developing Dementia.

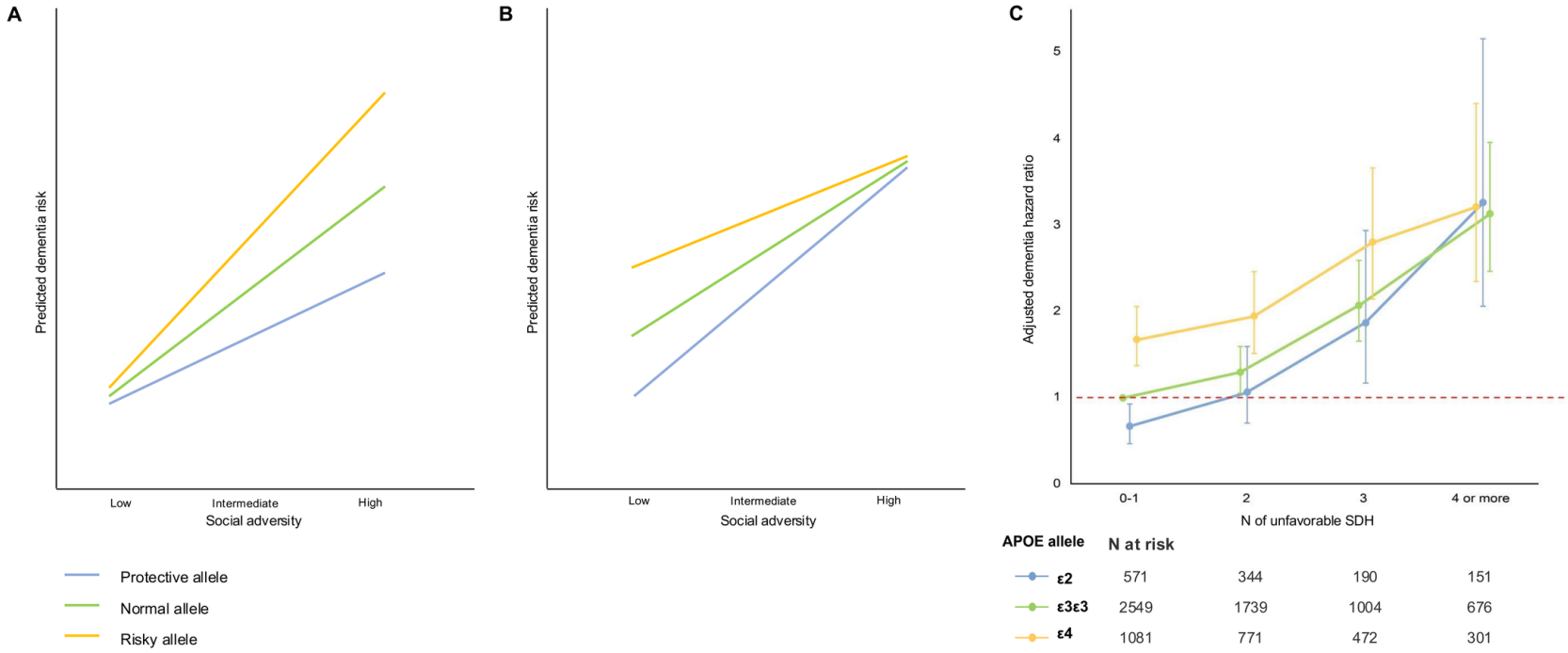

Figure 1. Theoretical Gene-Environmental Models and Actual Results with HRS and ELSA Participants Illustrating Social Adversity and APOE Allele Interactions to Determine Risk of Developing Dementia. Figures illustrating the Social Trigger Theoretical Model (A) and the Social Distinction Theoretical Model (B) for explaining the gene-environment interaction on cognitive health. Figure C describe the dementia Hazard Ratio by APOE allele profile and number of unfavorable social determinants of health (SDH) exposure compared to people at intermediate genetic risk (APOE-ε3ε3) exposed at 0-1 unfavorable SDH. APOE-ε2: ε2ε2, ε2ε3; APOE-ε4: ε2ε4, ε3ε4, ε4ε4. Figure C was designed based on our analyses performed with the pooled HRS and ELSA samples. N of unfavorable SDH exposed: less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical

disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

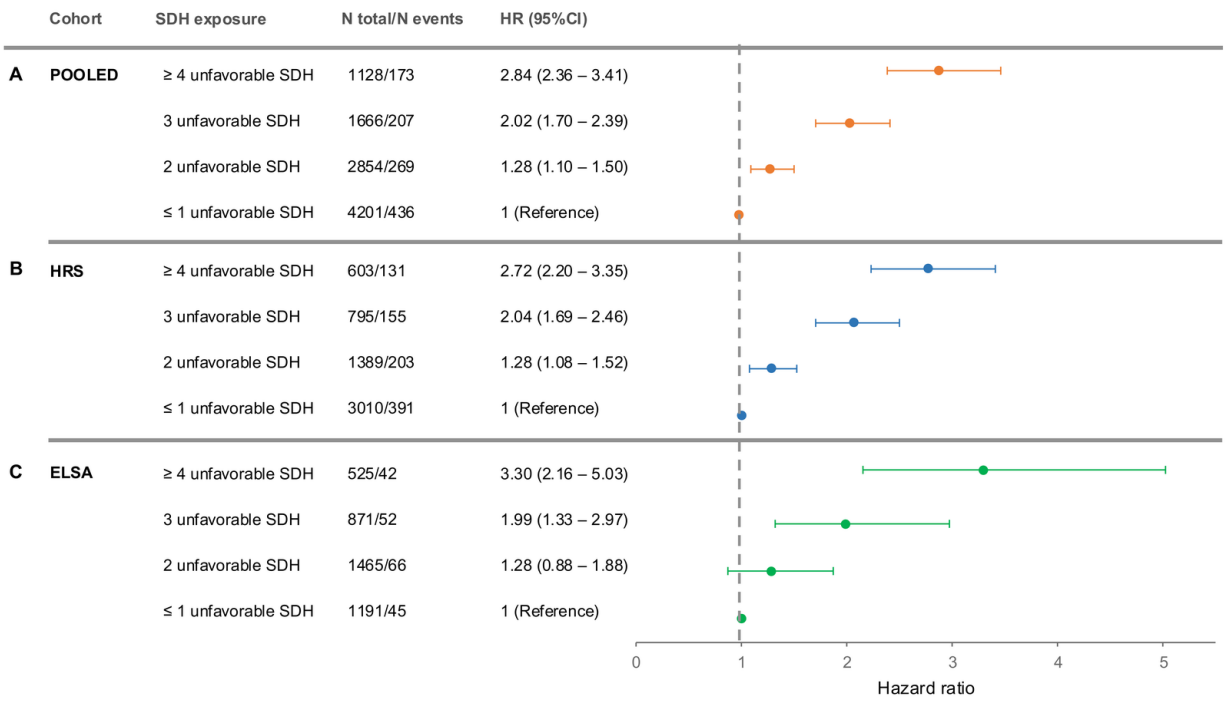

Figure 2. Association Between Social Adversity Level and Greater Risk of Dementia. Forest-plot for fully adjusted dementia Hazard ratio (HR) by exposure to number of unfavorable social determinants of health (SDH) (social adversity) in the population by pooled sample (A), the U.S. cohort and (B), the England cohort (C). Unfavorable SDH exposed: less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

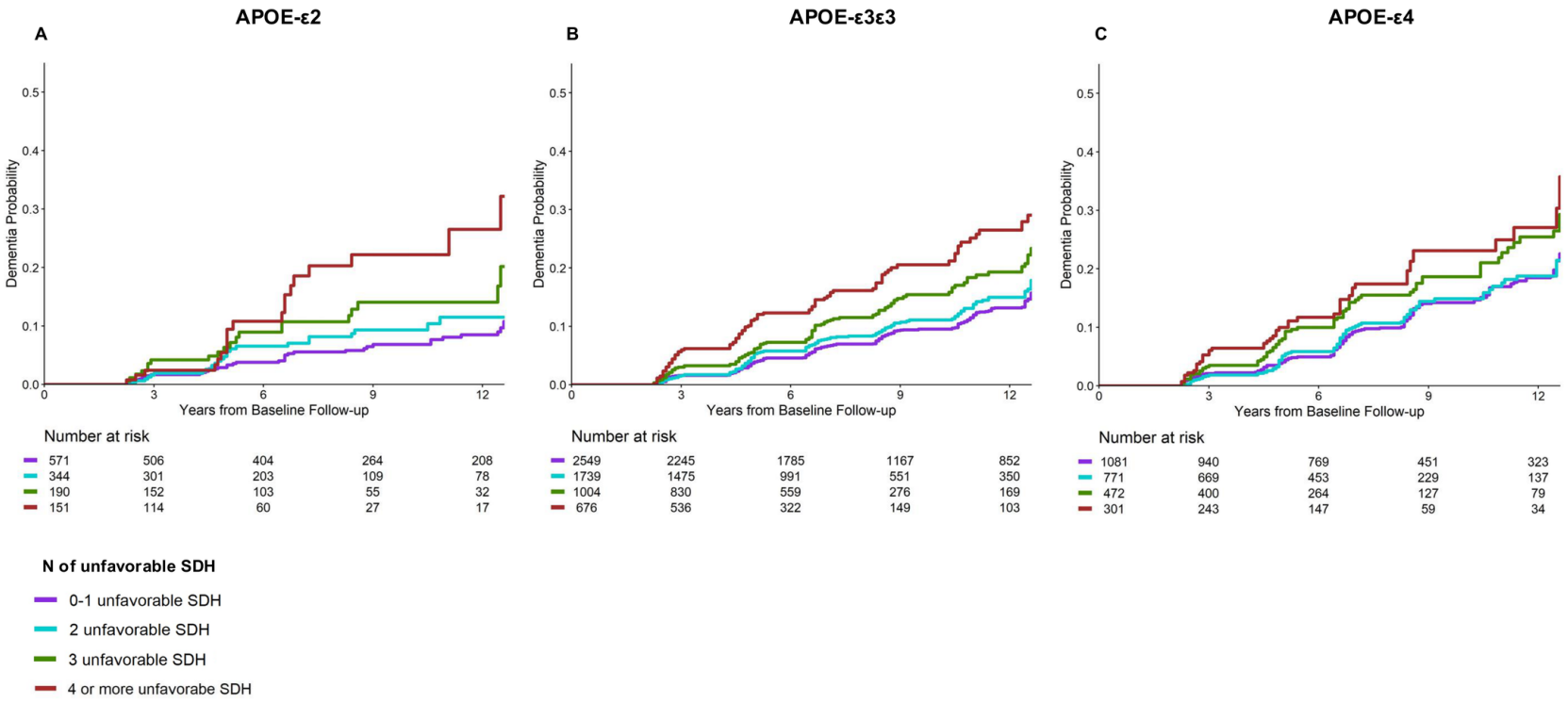

Figure 3. Cumulative Incidence of Dementia and Social Adversity Level by APOE Risk Profile. Unadjusted Kaplan-Meier survival curve for dementia incidence in people exposed to levels of social adversity (number of unfavorable social determinants of health -SDH-) in the pooled sample at low genetic risk (APOE-ε2ε2, ε2ε3)(A), intermediate genetic risk (APOE-ε3ε3)(B), and high genetic risk (APOE-ε2ε4, ε3ε4, ε4ε4)(C). N of unfavorable SDH exposed: less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Table 1. Descriptive Statistics of the Sample at Baseline by APOE Allele Risk Profile.

	Total sample n: 9849	**Low risk (APOE-ε2ε2, ε2ε3) n: 1256**	**Intermediate risk (APOE-ε3ε3) n: 5968**	**High risk (APOE-ε2ε4, ε3ε4, ε4ε4) n: 2625**	**P-value**
Follow-up duration in years Mean, SD (IQR)	6.88, 3.792 (4.0 – 10.0)	6.94, 3.867 (4.0 – 12.0)	6.90, 3.817 (4.0 – 10.0)	6.79, 3.702 (4.0 – 10.0)	0.371
Age Mean, SD (IQR)	68.45, 8.783 (62.0 – 74.0)	68.64, 8.922 (62.0 – 75.0)	68.68, 8.852 (62.0 – 75.0)	67.82, 8.527 (61.0 – 73.0)	<0.001
Sex n (%)					
Male	4404 (44.7)	554 (44.1)	2689 (45.1)	1161 (44.2)	0.698
Female	5445 (55.3)	702 (55.9)	3279 (54.9)	1464 (55.8)	
Race/ethnicity, n (%)					
Non-Hispanic White	8832 (89.7)	1132 (90.1)	5406 (90.6)	2294 (87.4)	<0.001
Non-Hispanic Black	766 (7.8)	104 (8.3)	394 (6.6)	268 (10.2)	
Other (American Indian, Alaskan Native, Asian, and Pacific Islander)	251 (2.5)	20 (1.6)	168 (2.8)	63 (2.4)	
Hispanic	454 (4.6)	30 (4.2)	320 (9.0)	104 (6.8)	
Dementia risk factors, n (%)					
Diabetes	1477 (15.0)	185 (14.7)	921 (15.4)	371 (14.1)	0.287
Hypertension	4954 (50.3)	616 (49.0)	3008 (50.4)	1330 (50.7)	0.619
Obesity	2959 (31.5)	387 (32.2)	1825 (32.0)	747 (29.8)	0.122
High-frequency drinking	1274 (13.0)	166 (13.3)	770 (13.0)	338 (13.0)	0.947
Physical inactivity	2252 (22.9)	291 (23.2)	1378 (23.1)	583 (22.2)	0.652
Smoking	1150 (11.7)	150 (12.0)	680 (11.4)	320 (12.2)	0.536
Hearing problems	435 (4.4)	53 (4.2)	273 (4.6)	109 (4.2)	0.635
Depression	1836 (18.6)	231 (18.4)	1127 (18.9)	478 (18.2)	0.729
N of dementia risk factors, n (%)					
0	1797 (18.2)	232 (18.5)	1086 (18.2)	479 (18.2)	0.977
1	3131 (31.8)	395 (31.4)	1888 (31.6)	848 (32.3)	
2	2512 (25.5)	323 (25.7)	1517 (25.4)	672 (25.6)	
≥3	2409 (24.5)	306 (24.3)	1475 (24.7)	626 (23.8)	
Social determinants of health					
Education level, n (%)					
Less than upper secondary	2066 (21.0)	247 (19.7)	1236 (20.7)	583 (22.2)	0.209

Upper secondary and vocational	5571 (56.6)	704 (56.1)	3398 (56.9)	1469 (56.0)	
Tertiary	2212 (22.5)	305 (24.3)	1334 (22.4)	573 (21.8)	
Family income quartile by cohort, n (%)					
<25th quartile income	2132 (21.6)	268 (21.3)	1296 (21.7)	568 (21.6)	0.998
25th – 75th quartile income	5120 (52.0)	656 (52.2)	3102 (52.0)	1362 (51.9)	
>75th quartile income	2597 (26.4)	332 (26.4)	1570 (26.3)	695 (26.5)	
Healthcare access, n (%)					
No private health insurance	4776 (48.5)	617 (49.1)	2932 (49.1)	1227 (46.7)	0.112
Healthcare discrimination	546 (5.5)	67 (5.3)	331 (5.5)	148 (5.6)	0.928
Neighborhood environment, n (%)					
Physical disorder					
Low (<25th)	2071 (21.0)	248 (19.7)	1242 (20.8)	581 (22.1)	0.331
Moderate (25th – 75th)	4614 (46.8)	585 (46.6)	2800 (46.9)	1229 (46.9)	
High (>75th)	3164 (32.2)	423 (33.7)	1926 (32.3)	815 (31.0)	
Social cohesion difficulties					
Low (<25th)	2079 (21.1)	267 (21.3)	1232 (20.6)	580 (22.1)	0.247
Moderate (25th – 75th)	4640 (47.1)	568 (45.2)	2829 (47.4)	1243 (47.4)	
High (>75th)	3130 (31.8)	421 (33.5)	1907 (32.0)	802 (30.6)	
Social and community context, n (%)					
Social support					
Low (<25th)	2221 (22.6)	259 (20.6)	1357 (22.7)	605 (23.0)	0.009
Moderate (25th – 75th)	5097 (51.8)	629 (50.1)	3076 (51.5)	1392 (53.0)	
High (>75th)	2531 (25.7)	368 (29.3)	1535 (25.7)	628 (23.9)	
N of types of discrimination					
0	4692 (47.6)	605 (48.2)	2850 (47.8)	1237 (47.1)	0.791
1	3358 (34.1)	432 (34.4)	2012 (33.7)	914 (34.8)	
≥2	1799 (18.3)	219 (17.4)	1106 (18.5)	474 (18.1)	
Social adversity: n of unfavorable SDH					
≤ 1	4201 (42.7)	571 (45.5)	2549 (42.7)	1081 (41.2)	0.143
2	2854 (29.0)	344 (27.4)	1739 (29.1)	771 (29.4)	

3	1666 (16.9)	190 (15.1)	1004 (16.8)	472 (18.0)	
≥ 4	1128 (11.4)	151 (12.0)	676 (11.3)	301 (11.5)	
Any functional limitations in ADL, n (%)	1340 (13.6)	169 (13.5)	826 (13.8)	345 (13.1)	0.676

SDH: Social Determinants of Health; IQR: interquartile range; ADL: Activities of daily living.
<25^{th}: less than 25^{th} quartile by cohort; 25^{th} – 75^{th}: between 25^{th} and 75^{th} quartile by cohort; >75^{th}: more than 75^{th} quartile by cohort.
Social adversity measured as N of unfavorable social determinants of health (SDH) exposed: Less than upper secondary education, being in the 25^{th} lower family income range, 25^{th} lower score in neighborhood physical disorder, 25^{th} lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25^{th} lower score in perceived social support, having experienced two or more different types of discrimination.
P-value for chi-square test (X^2) for nominal and ordinal variables and ANOVA test for continuous variables comparison.

Table 2. Interaction Between Social Adversity Level and APOE Allele Risk Profile on Greater Dementia Risk.

		ELSA		HRS		Pooled analysis with ELSA and HRS
APOE allele risk profile	**N of unfavorable SDH**	**N total / N events**	**HR (95%CI)**	**N total / N events**	**HR (95%CI)**	**HR (95%CI)**
Low risk (ε2ε2, ε2ε3)	**≤ 1 SDH**	168/2	0.28 (0.07 – 1.18)	403/37	0.72 (0.51 – 1.02)	0.67 (0.48 – 0.93) **
	2 SDH	186/8	1.16 (0.53 – 2.56)	158/18	0.99 (0.61 – 1.61)	1.06 (0.71 – 1.59)
	3 SDH	113/8	2.01 (0.91 – 4.43)	77/12	1.67 (0.93 – 2.98)	1.85 (1.17 – 2.93) **
	≥ 4 SDH	82/4	1.77 (0.62 – 5.07)	69/16	3.78 (2.26 – 6.31) ***	3.26 (2.06 – 5.16) ***
Intermediate risk (ε3ε3)	**≤ 1 SDH**	704/28	Ref	1845/222	Ref	Ref
	2 SDH	878/36	1.08 (0.65 – 1.78)	861/118	1.33 (1.06 – 1.66) **	1.30 (1.06 – 1.59) **
	3 SDH	527/28	1.85 (1.09 – 3.15) *	477/89	2.10 (1.64 – 2.70) ***	2.07 (1.66 – 2.59) ***
	≥ 4 SDH	301/23	3.26 (1.87 – 5.71) ***	375/82	3.03 (2.34 – 3.94) ***	3.12 (2.47 – 3.95) ***
High risk (ε2ε4, ε3ε4, ε4ε4)	**≤ 1 SDH**	319/16	1.36 (0.73 – 2.52)	762/132	1.71 (1.38 – 2.12) ***	1.68 (1.37 – 2.06) ***
	2 SDH	401/22	1.77 (1.01 – 3.11) *	370/67	1.95 (1.48 – 2.57) ***	1.93 (1.51 – 2.46) ***
	3 SDH	231/16	2.10 (1.13 – 3.90) **	241/54	2.99 (2.21 – 4.04) ***	2.80 (2.14 – 3.66) ***
	≥ 4 SDH	142/15	4.09 (2.17 – 7.71) ***	159/33	2.88 (1.98 – 4.19) ***	3.21 (2.34 – 4.41) ***

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; Ref: reference value.
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

All models were adjusted by age, sex, and race. The pooled model was additionally adjusted by cohort (HRS or ELSA). Random effect (I^2) for the pooled model: 0.0%
Social adversity measured as N of unfavorable SDH exposed: less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.
Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). The variables meet the hazard proportionality assumption (p-value >0.05).

Table 3. Association Between Social Adversity Level and Greater Dementia Risk by APOE Allele Risk Profile.

		ELSA		HRS		Pooled analysis with ELSA and HRS
APOE allele risk profile	**N of unfavorable SDH**	**N at risk / N event**	**HR (95%CI)**	**N at risk / N event**	**HR (95%CI)**	**HR (95%CI)**
Low risk (ε2ε2, ε2ε3)	**≤ 1 SDH**	168/2	Ref	403/37	Ref	Ref
	2 SDH	186/8	4.08 (0.86 – 19.34)	158/18	1.33 (0.75 – 2.35)	1.55 (0.93 – 2.57)
	3 SDH	113/8	7.48 (1.58 – 35.34) **	77/12	2.23 (1.15 – 4.30) **	2.74 (1.58 – 4.76) ***
	≥ 4 SDH	82/4	6.37 (1.14 – 35.49) **	69/16	4.75 (2.51 – 8.99) ***	4.47 (2.52 – 7.94) ***
	p-for trend	0.021		<0.001		<0.001
Intermediate risk (ε3ε3)	**≤ 1 SDH**	704/28	Ref	1845/222	Ref	Ref
	2 SDH	878/36	1.06 (0.64 – 1.75)	861/118	1.31 (1.05 – 1.64) **	1.27 (1.04 – 1.56) *
	3 SDH	527/28	1.79 (1.05 – 3.05) *	477/89	2.08 (1.61 – 2.67) ***	2.03 (1.62 – 2.55) ***
	≥ 4 SDH	301/23	3.23 (1.85 – 5.66) ***	375/82	2.95 (2.26 – 3.85) ***	3.03 (2.39 – 3.86) ***
	p-for trend	<0.001		<0.001		<0.001
High risk (ε2ε4, ε3ε4, ε4ε4)	**≤ 1 SDH**	319/16	Ref	762/132	Ref	Ref
	2 SDH	401/22	1.32 (0.69 – 2.52)	370/67	1.18 (0.88 – 1.59)	1.19 (0.91 – 1.55)
	3 SDH	231/16	1.58 (0.79 – 3.17)	241/54	1.84 (1.33 – 2.54) ***	1.76 (1.31 – 2.35) ***
	≥ 4 SDH	142/15	3.14 (1.55 – 6.40) ***	159/33	1.86 (1.24 – 2.78) **	2.09 (1.48 – 2.95) ***
	p-for trend	0.001		<0.001		<0.001

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; Ref: reference value; p-for trend: p-value for linear trend.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort (HRS or ELSA). Random effects (I^2) for the three pooled models: 0.0%
Social adversity measured as N of unfavorable SDH exposed: less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.
Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). The variables meet the hazard proportionality assumption (p-value >0.05).

Supporting information

S1. STROBE Statement—Checklist of items that should be included in reports of cohort studies.

S2. Social determinants of health and genetic data measurement.

S1 Table. Descriptive characteristics of ELSA and HRS sample included at baseline.

S2 Table. Analysis of social advantage on the risk of dementia according to APOE allele risk profile.

S3 Table. Analysis of social adversity on the risk of dementia according to polygenic risk score of AD profile.

S4 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile excluding people with mild cognitive impairment.

S5 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile in dementia cases identified using cognitive and functional impairment only.

S6 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile adjusting by the number of dementia risk factors.

S7 Table. Descriptive statistics of ELSA and HRS sample included and excluded based on complete social determinants of health information available at baseline.

S8 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile weighting by the inverse probability of being selected in the study.

S9 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile by sex.

S10 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile by race.

S11 Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile by individual social determinants.

S1 Fig. Participant's study selection for HRS and ELSA populations.

S2 Fig. Social advantage Interacts with APOE Allele to Determine Risk of Developing Dementia.

S1. STROBE Statement—Checklist of items that should be included in reports of *cohort studies.*

	Item No	Recommendation	Page included
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	9-10
		(*e*) Describe any sensitivity analyses	10-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	3

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	S.1, S.7
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	F.1, F.3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	T.2, T.3
		(*b*) Report category boundaries when continuous variables were categorized	T.2, T.3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14,15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

S2. Social determinants of health and genetic data measurement.

Social determinants of health measurement

Education access was measured through educational level divided into three levels for cross-national comparison: less than upper secondary school, upper secondary and vocational, and tertiary education.(1) Economic stability was measured with the mean family income, categorizing people into three groups based on each sample (HRS and ELSA) populational quartile family income: low family income (<25th quartile), intermediate family income (25th to 75th quartile), high family income (>75th quartile).(2) The neighborhood environment was assessed using a measurement scale for perceived neighborhood physical disorder (three items) and social cohesion (four items) with a Likert scale ranging from 1 “Very positive” to 7 “Very negative”;(2) Neighborhood physical disorder and social cohesion were divided into three categories each, according to population quartile scores: low (<25th quartile), intermediate (25th – 75th quartile), and high (>75th quartile). Healthcare access and quality were measured through two questions: a) if people have any type of private healthcare insurance (Yes/No), and b) if they have experienced healthcare discrimination in the last year, understood as ‘a poorer service than other people from doctors or hospitals’(3) (Yes/No). Social context was measured through two variables. The first was mean social support: a Liker format scale ranging from one (“Low support”) to four (“High support”), that assesses perceived children support (six items), spouse/couple support (seven items), and other family members support (seven items).(2) The mean score among children, spouse/couple, and family members' support was calculated and then divided into three categories according to every sample quartile score: low social support (<25th quartile), intermediate (25th to 75th quartile), and high (>75th quartile). The second was the number of discrimination types experienced, divided into three levels for increasing sample size per level: no discrimination experienced, one discrimination type, or two or more types of discrimination experienced.

Genetic information measurement

Genetic data was collected in 2006, 2008, and 2010 in the HRS sample. APOE was measured using saliva sample and genotyped using the Illumina Human Omni-2.5-4v1 and Illumina Human Omni-2.5-8v1 Quad BeadChips.(4) Missing call rates of more than 5% and minor allele frequency of less than 5% were used to filter autosomal SNPs. Imputation was performed using the 1000 Genomes Project imputation. European and African genetic ancestry were identified through principal component analysis on independent genome-wide SNPs, with a perfect correlation between genetic ancestry and self-reported race/ethnicity.(5)

Genetic data was collected in 2004-2005 in the ELSA sample. APOE is measured using a blood sample and the Illumina HumanOmni2.5 BeadChips (HumanOmni2.5-4v1, HumanOmni2.5-8v1.3) to genotype the data.(6) Genotyping was performed in two batches. After filtering for 5% of missingness, allele frequency was compared between batches, with correlation overcoming 99%. Imputation was performed using SHAPEIT for pre-phasing, and Minimac3 for imputation using the Haplotype Reference Consortium (HRC.r1-1.GRCh37).(6)

Genetic variants used for identifying APOE allele were rs7412 and rs429358. Individuals of both studies were classified according to their APOE risk profile as low risk (APOE-ε2ε2 or ε2ε3 carriers), intermediate risk (APOE-ε3ε3 carriers), or high risk (APOE-ε2ε4, ε3ε4, or ε4ε4 carriers).

For sensitivity analyses, a polygenic risk score (PGS) for AD dementia that did not include the APOE allele was used. For both samples, the PGS was created using the results from a 2013 GWAS meta-analysis conducted by the International Genomics of Alzheimer's Project (IGAP), that included 20 independent studies using data from four international cohorts.(7) The methods for the construction of PGS for AD in both samples have been previously described in detail.(8,9) Participants were classified according to their PGS for AD dementia score by cohort

and ancestry in three groups: low risk (< 25th quartile score), intermediate risk (25th - 75th quartile score), and high risk (> 75th quartile score) of dementia.

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S1 Table. Descriptive statistics of ELSA and HRS sample included at baseline.

	ELSA (n: 4,052)	HRS (n: 5,797)	P-value
Follow-up duration in years Mean, SD (IQR)	4.86, 2.418 (4 – 8)	8.27, 3.940 (6 – 12)	2.2e-16
Age Mean, SD (IQR)	67.99, 8.208 (62 – 73)	68.76, 9.150 (61 – 75)	2.009e-05
Sex n (%)			
Male	1910 (47.1%)	2494 (43.0%)	5.304e-05
Female	2142 (52.9%)	3303 (57.0%)	
Race/ethnicity n (%)			
Non-Hispanic White	4051 (99.9%)	4781 (82.5%)	NA
Non-Hispanic Black	0	766 (13.2%)	
Other (American Indian, Alaskan Native, Asian, and Pacific Islander)	1 (0.1%)	250 (4.3%)	
Hispanic	0	454 (7.8%)	
Dementia risk factors n (%)			
Diabetes	378 (9.3%)	1099 (19.0%)	2.2e-16
Hypertension	1743 (43.0%)	3211 (55.4%)	2.2e-16
Obesity	1134 (30.9%)	1825 (31.9%)	0.3038
High-frequency drinking	739 (18.6%)	535 (9.5%)	2.2e-16
No or little participation in physical activity	785 (19.4%)	1467 (25.3%)	4.356e-12
Smoking	433 (10.7%)	717 (12.4%)	0.007835
Hearing problems	162 (4.0%)	273 (4.7%)	0.09002
Depression	737 (18.2%)	1099 (19.0%)	0.3363
N of dementia risk factors n (%)			
0	866 (21.4%)	931 (16.1%)	2.2e-16
1	1378 (34.0%)	1753 (30.2%)	
2	999 (24.7%)	1513 (26.1%)	
≥3	809 (19.9%)	1600 (27.6%)	
Social determinants of health			
Education level n (%)			
Less than upper secondary	1228 (30.3%)	984 (17.0%)	2.2e-16
Upper secondary and vocational	2085 (51.5%)	3486 (60.1%)	
Tertiary	739 (18.2%)	1327 (22.9%)	
Family income quartile by cohort n (%)			
<25th quartile income	902 (22.3%)	1230 (21.2%)	0.4651
25th – 75th quartile income	2089 (51.6%)	3031 (52.3%)	
>75th quartile income	1061 (26.2%)	1536 (26.5%)	
Healthcare access n (%)			
No private health insurance	3519 (86.8%)	1554 (26.8%)	2.2e-16
Healthcare discrimination	168 (4.1%)	378 (6.5%)	4.029e-07
Neighborhood environment n (%)			
Physical disorder			
Low (<25th)	1341 (33.1%)	1823 (31.4%)	1.3e-12
Moderate (25th – 75th)	2005 (49.5%)	2609 (45.0%)	
High (>75th)	706 (17.4%)	1365 (23.5%)	
Social cohesion difficulties			
Low (<25th)	1236 (30.5%)	1894 (32.7%)	1.27e-12
Moderate (25th – 75th)	2076 (51.2%)	2564 (44.2%)	
High (>75th)	740 (18.3%)	1339 (23.1%)	
Social and community context n (%)			
Social support			

Low (<25th)	865 (21.3%)	1356 (23.4%)	0.0001346
Moderate (25th – 75th)	2200 (54.3%)	2897 (50.0%)	
High (>75th)	987 (24.4%)	1544 (26.6%)	
N of types of discrimination experienced			
0	2261 (55.8%)	2431 (41.9%)	2.2e-16
1	1178 (29.1%)	2180 (37.6%)	
≥2	613 (15.1%)	1186 (20.5%)	
N of unfavorable SDH exposed			
0 – 1	1191 (29.4%)	3010 (51.9%)	2.2e-16
2	1465 (36.2%)	1389 (24.0%)	
3	871 (21.5%)	795 (13.7%)	
≥ 4	525 (13.0%)	603 (10.4%)	
APOE allele dosage			
e2e2	20 (0.4%)	32 (0.6%)	2.2e-16
e2e3	529 (13.1%)	675 (11.6%)	
e2e4	0	135 (1.4%)	
e3e3	2410 (59.5%)	3558 (61.4%)	
e3e4	916 (22.6%)	1271 (21.9%)	
e4e4	177 (4.4%)	126 (2.2%)	
Overall APOE dosage			
e2 (e2e2, e2e3)	549 (13.5%)	707 (12.2%)	0.07765
e3e3	2410 (59.5%)	3558 (61.4%)	
e4 (e2e4, e3e4, e4e4)	1093 (27.0%)	1532 (26.4%)	
Any functional limitations in ADL n (%)	554 (13.7%)	786 (13.6%)	0.8715

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; IQR: interquartile range; NA: not applicable.

<25th: less than 25th quartile by cohort; 25th – 75th: between 25th and 75th quartile by cohort; >75th: more than 75th quartile by cohort.

P-value for chi-square test (X^2) for nominal and ordinal variables and ANOVA test for continuous variables compariso

S2.a Table. Analysis of social advantage on the risk of dementia according to APOE allele risk profile.							
		ELSA		HRS		Fully adjusted Pooled analysis	I^2
APOE dosage	**N of favorable SDH**	**N at risk / N event**	**HR (95%CI), p-value**	**N at risk / N event**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	
e2	**≤ 1 SDH**	68/3	Ref	42/7	Ref	Ref	
	2 SDH	141/7	1.17 (0.30 – 4.55)	149/16	0.76 (0.31 – 1.87)	0.86 (0.41 – 1.81)	0.0%
	3 SDH	157/6	0.66 (0.16 – 2.64)	169/27	0.89 (0.38 – 2.04)	0.84 (0.41 – 1.71)	
	≥ 4 SDH	183/6	0.70 (0.17 – 2.83)	347/33	0.43 (0.19 – 0.98) *	0.45 (0.22 – 0.92) *	
e3e3	**≤ 1 SDH**	824/36	Ref	225/40	Ref	Ref	
	2 SDH	1013/44	0.51 (0.28 – 0.93) *	735/111	0.64 (0.44 – 0.92) *	0.60 (0.44 – 0.82) **	0.0%
	3 SDH	453/28	0.56 (0.31 – 1.01)	958/140	0.57 (0.40 – 0.80) **	0.57 (0.42 – 0.76) ***	
	≥ 4 SDH	109/5	0.60 (0.35 – 1.02)	1640/220	0.45 (0.32 – 0.63) ***	0.47 (0.35 – 0.62) ***	
e4	**≤ 1 SDH**	156/14	Ref	96/25	Ref	Ref	
	2 SDH	295/17	0.51 (0.25 – 1.05)	350/61	0.61 (0.38 – 0.97) *	0.59 (0.40 – 0.87) **	0.0%
	3 SDH	302/12	0.33 (0.15 – 0.72) **	417/76	0.62 (0.39 – 0.97) *	0.56 (0.38 – 0.81) **	
	≥ 4 SDH	340/26	0.49 (0.25 – 0.96) *	669/124	0.53 (0.34 – 0.81) **	0.52 (0.37 – 0.75) ***	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social advantage measured as N of favorable SDH exposed: Tertiary education, being in the 75th higher family income range, 75th higher score in neighborhood physical disorder, 75th higher score in neighborhood social cohesion, no experiences of doctors' or hospitals' poorer health service, having some private healthcare insurance, 75th higher score in perceived social support, no experiences of any type of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S2.b Table. Analysis of social advantage on the risk of dementia according to APOE allele risk profile.							
		ELSA		HRS		Fully adjusted pooled analysis	I^2
APOE dosage	**N of favorable SDH**	**N total / N events**	**HR (95%CI), p-value**	**N total / N events**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	0.0%
e2	**≤ 1 SDH**	68/3	0.58 (0.17 – 1.94)	42/7	0.72 (0.32 – 1.60)	0.68 (0.35 – 1.34)	
	2 SDH	141/7	0.73 (0.31 – 1.73)	149/16	0.52 (0.29 – 0.92) *	0.57 (0.35 – 0.91) *	
	3 SDH	157/6	0.40 (0.16 – 0.99) *	169/27	0.60 (0.37 – 0.98) *	0.55 (0.36 – 0.85) **	
	≥ 4 SDH	183/6	0.38 (0.15 – 0.94) *	347/33	0.28 (0.18 – 0.45) ***	0.29 (0.19 – 0.43) ***	
e3e3	**≤ 1 SDH**	824/36	Ref	225/40	Ref	Ref	
	2 SDH	1013/44	0.51 (0.28 – 0.93) *	735/111	0.65 (0.45 – 0.93) *	0.61 (0.45 – 0.83) **	
	3 SDH	453/28	0.56 (0.31 – 1.00)	958/140	0.57 (0.40 – 0.81) **	0.56 (0.42 – 0.76) ***	
	≥ 4 SDH	109/5	0.60 (0.35 – 1.02)	1640/220	0.45 (0.32 – 0.63) ***	0.47 (0.35 – 0.62) ***	
e4	**≤ 1 SDH**	156/14	1.61 (0.81 – 3.19)	96/25	1.29 (0.78 – 2.12)	1.34 (0.90 – 2.01)	
	2 SDH	295/17	0.89 (0.46 – 1.70)	350/61	0.81 (0.54 – 1.20)	0.81 (0.58 – 1.14)	
	3 SDH	302/12	0.59 (0.29 – 1.21)	417/76	0.82 (0.56 – 1.21)	0.77 (0.55 – 1.07)	
	≥ 4 SDH	340/26	0.81 (0.45 – 1.45)	669/124	0.73 (0.51 – 1.05)	0.75 (0.55 – 1.01)	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social advantage measured as N of favorable SDH exposed: Tertiary education, being in the 75th higher family income range, 75th higher score in neighborhood physical disorder, 75th higher score in neighborhood social cohesion, no experiences of doctors' or hospitals' poorer health service, having some private healthcare insurance, 75th higher score in perceived social support, no experiences of any type of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S3.a Table. Analysis of social adversity on the risk of dementia according to polygenic risk score of AD profile.							
		ELSA		HRS		Fully adjusted Pooled analysis	I^2
Polygenic risk score	**N of SDH**	**N at risk / N event**	**HR (95%CI), p-value**	**N at risk / N event**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	
< 25th	**≤ 1 SDH**	286/6	Ref	734/98	Ref	Ref	
	2 SDH	365/11	1.32 (0.49 – 3.59)	310/39	1.00 (0.68 – 1.45)	1.04 (0.73 – 1.46)	0.0%
	3 SDH	238/9	2.13 (0.76 – 5.99)	150/30	1.92 (1.25 – 2.94) **	1.91 (1.29 – 3.81) **	
	≥ 4 SDH	141/11	5.82 (2.14 – 15.88) ***	97/21	2.40 (1.43 – 4.06) **	2.96 (1.91 – 4.60) ***	
25th – 75th	**≤ 1 SDH**	619/30	Ref	1346/168	Ref	Ref	
	2 SDH	713/33	1.11 (0.67 – 1.83)	571/75	1.16 (0.88 – 1.52)	1.16 (0.93 – 1.47)	0.0%
	3 SDH	427/26	1.52 (0.89 – 2.61)	300/56	2.16 (1.59 – 2.93) ***	1.98 (1.52 – 2.58) ***	
	≥ 4 SDH	248/18	2.32 (1.29 – 4.19) **	224/50	2.82 (2.03 – 3.91) ***	2.69 (2.02 – 3.58) ***	
>75th	**≤ 1 SDH**	286/9	Ref	636/85	Ref	Ref	
	2 SDH	387/22	1.86 (0.84 – 4.01)	278/49	1.83 (1.28 – 2.63) ***	1.73 (1.25 – 2.40) ***	0.0%
	3 SDH	206/17	3.43 (1.52 – 7.72) **	162/27	1.84 (1.18 – 2.88) **	2.14 (1.47 – 3.11) ***	
	≥ 4 SDH	136/13	4.73 (2.00 – 11.17) ***	108/23	2.32 (1.39 – 3.86) **	2.88 (1.89 – 4.39) ***	
P for interaction			0.2511		0.268	0.533	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S3.b Table. Analysis of social adversity on the risk of dementia according to polygenic risk score of AD profile.							
		ELSA		HRS		Fully adjusted pooled analysis	I^2
Polygenic score	**N of SDH**	**N total / N events**	**HR (95%CI), p-value**	**N total / N events**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	0.0%
< 25th	**≤ 1 SDH**	286/6	0.49 (0.20 – 1.18)	734/98	1.07 (0.84 – 1.38)	0.99 (0.78 – 1.26)	
	2 SDH	365/11	0.69 (0.35 – 1.38)	310/39	1.04 (0.73 – 1.47)	0.96 (0.70 – 1.31)	
	3 SDH	238/9	1.09 (0.52 – 2.31)	150/30	2.02 (1.37 – 2.99) ***	1.75 (1.23 – 2.47) **	
	≥ 4 SDH	141/11	2.78 (1.39 – 5.58) **	97/21	2.48 (1.56 – 3.95) ***	2.64 (1.81 – 3.87) ***	
25th – 75th	**≤ 1 SDH**	619/30	Ref	1346/168	Ref	Ref	
	2 SDH	713/33	1.13 (0.69 – 1.85)	571/75	1.15 (0.88 – 1.51)	1.17 (0.92 – 1.48)	
	3 SDH	427/26	1.54 (0.91 – 2.62)	300/56	2.14 (1.58 – 2.91) **	1.99 (1.53 – 2.59) ***	
	≥ 4 SDH	248/18	2.24 (1.25 – 4.02) **	224/50	2.74 (1.98 – 3.78) ***	2.66 (2.01 – 3.53) ***	
>75th	**≤ 1 SDH**	286/9	0.71 (0.34 – 1.51)	636/85	0.98 (0.75 – 1.27)	0.94 (0.73 – 1.20)	
	2 SDH	387/22	1.25 (0.72 – 2.18)	278/49	1.87 (1.36 – 2.57) ***	1.72 (1.31 – 2.26) ***	
	3 SDH	206/17	2.48 (1.37 – 4.51) **	162/27	1.88 (1.25 – 2.82) **	2.11 (1.52 – 2.94) ***	
	≥ 4 SDH	136/13	3.68 (1.91 – 7.08) ***	108/23	2.59 (1.66 – 4.04) ***	2.98 (2.08 – 4.29) ***	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S4.a Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile excluding people with mild cognitive impairment.							
		ELSA (n: 3,852)		HRS (n: 5,503)		Fully adjusted Pooled analysis	I^2
APOE dosage	**N of SDH**	**N at risk / N event**	**HR (95%CI), p-value**	**N at risk / N event**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	
e2	**≤ 1 SDH**	167/2	Ref	394/32	Ref	Ref	
	2 SDH	174/7	4.06 (0.84 – 19.64)	149/16	1.38 (0.75 – 2.55)	1.62 (0.94 – 2.78)	0.0%
	3 SDH	105/7	6.98 (1.45 – 33.70) *	67/9	2.14 (1.02 – 4.50) *	2.72 (1.48 – 4.99) **	
	≥ 4 SDH	79/3	5.10 (0.84 – 31.05)	57/12	5.88 (2.90 – 11.96) ***	4.90 (2.59 – 9.28) ***	
e3e3	**≤ 1 SDH**	685/23	Ref	1805/205	Ref	Ref	
	2 SDH	839/25	0.91 (0.52 – 1.61)	817/99	1.25 (0.98 – 1.59)	1.19 (0.95 – 1.49)	0.0%
	3 SDH	501/21	1.69 (0.93 – 3.08)	448/80	2.18 (1.68 – 2.84) ***	2.10 (1.65 – 2.68) ***	
	≥ 4 SDH	281/18	3.14 (1.69 – 5.85) ***	333/62	2.77 (2.06 – 3.73) ***	2.88 (2.21 – 3.76) ***	
e4	**≤ 1 SDH**	301/14	Ref	731/119	Ref	Ref	
	2 SDH	376/18	1.32 (0.65 – 2.67)	353/61	1.21 (0.89 – 1.65)	1.20 (0.91 – 1.59)	0.0%
	3 SDH	214/15	1.70 (0.82 – 3.52)	211/43	1.81 (1.27 – 2.57) **	1.75 (1.28 – 2.40) ***	
	≥ 4 SDH	130/15	3.73 (1.79 – 7.78) ***	138/25	1.68 (1.06 – 2.65) *	2.09 (1.44 – 3.04) ***	
P for interaction			0.7358		0.0026	0.00467	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Mild cognitive impairment defines as

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S4.b Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile excluding people with mild cognitive impairment.							
		ELSA (n: 3,852)		HRS (n: 5,503)		Fully adjusted pooled analysis	I^2
APOE dosage	**N of SDH**	**N total / N events**	**HR (95%CI), p-value**	**N total / N events**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	0.0%
e2	**≤ 1 SDH**	167/2	0.32 (0.07 – 1.35)	394/32	0.68 (0.47 – 0.98) *	0.63 (0.44 – 0.91) *	
	2 SDH	174/7	1.25 (0.54 – 2.92)	149/16	0.97 (0.58 – 1.62)	1.06 (0.69 – 1.63)	
	3 SDH	105/7	2.08 (0.89 – 4.86)	67/9	1.47 (0.75 – 2.87)	1.74 (1.05 – 2.89) *	
	≥ 4 SDH	79/3	1.61 (0.48 – 5.37)	57/12	4.24 (2.36 – 7.62) ***	3.38 (2.00 – 5.73) ***	
e3e3	**≤ 1 SDH**	685/23	Ref	1805/205	Ref	Ref	
	2 SDH	839/25	0.94 (0.53 – 1.66)	817/99	1.25 (0.99 – 1.60)	1.20 (0.96 – 1.49)	
	3 SDH	501/21	1.76 (0.97 – 3.19)	448/80	2.19 (1.69 – 2.84) ***	2.10 (1.66 – 2.67) ***	
	≥ 4 SDH	281/18	3.16 (1.70 – 5.87) ***	333/62	2.80 (2.10 – 3.75) ***	2.91 (2.24 – 3.78) ***	
e4	**≤ 1 SDH**	301/14	1.45 (0.75 – 2.83)	731/119	1.70 (1.35 – 2.13) ***	1.68 (1.35 – 2.08) ***	
	2 SDH	376/18	1.91 (1.03 – 3.55) *	353/61	2.01 (1.51 – 2.68) ***	1.99 (1.54 – 2.58) ***	
	3 SDH	214/15	2.38 (1.24 – 4.56) **	211/43	2.98 (2.14 – 4.16) ***	2.86 (2.14 – 3.84) ***	
	≥ 4 SDH	130/15	5.11 (2.66 – 9.81) ***	138/25	2.64 (1.72 – 4.05) ***	3.27 (2.32 – 4.63) ***	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Mild cognitive impairment defined as

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S5.a Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile in dementia cases identified using cognitive and functional impairment only.							
		ELSA (n: 4,051)		HRS (n: 5,792)		Fully adjusted Pooled analysis	I^2
APOE dosage	**N of SDH**	**N at risk / N event**	**HR (95%CI), p-value**	**N at risk / N event**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	
e2	**≤ 1 SDH**	168/2	Ref	403/33	Ref	Ref	
	2 SDH	186/6	3.17 (0.64 – 15.79)	158/13	1.04 (0.54 – 2.00)	1.24 (0.70 – 2.19)	0.0%
	3 SDH	113/8	7.74 (1.64 – 36.56) **	77/12	2.48 (1.27 – 4.84) **	2.68 (1.48 – 4.87) ***	
	≥ 4 SDH	82/3	5.26 (0.86 – 32.10)	69/16	5.17 (2.68 – 9.95) ***	4.60 (2.53 – 8.35) ***	
e3e3	**≤ 1 SDH**	703/15	Ref	1845/181	Ref	Ref	
	2 SDH	878/25	1.29 (0.68 – 2.44)	859/97	1.31 (1.02 – 1.69) *	1.30 (1.03 – 1.64) *	0.0%
	3 SDH	527/21	2.20 (1.13 – 4.29) *	477/71	1.99 (1.51 – 2.64) ***	2.03 (1.58 – 2.62) ***	
	≥ 4 SDH	301/20	4.84 (2.47 – 9.48) ***	375/77	3.38 (2.55 – 4.48) ***	3.60 (2.78 – 4.66) ***	
e4	**≤ 1 SDH**	319/7	Ref	762/91	Ref	Ref	
	2 SDH	401/11	1.43 (0.55 – 3.72)	368/48	1.20 (0.84 – 1.70)	1.21 (0.87 – 1.68)	0.0%
	3 SDH	231/8	1.72 (0.62 – 4.77)	240/45	2.12 (1.47 – 3.05) ***	2.01 (1.43 – 2.83) ***	
	≥ 4 SDH	142/11	4.87 (1.87 – 12.68) **	159/29	2.14 (1.37 – 3.34) ***	2.53 (1.71 – 3.75) ***	
P for interaction			0.944		0.0110	0.009334	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Dementia defined according to

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S5.b Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile in dementia cases identified using cognitive and functional impairment only.							
		ELSA		HRS		Fully adjusted pooled analysis	I^2
APOE dosage	N of SDH	N total / N events	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	HR (95%CI), p-value	0.0%
e2	0 SDH	168/2	0.52 (0.12 – 2.27)	403/33	0.77 (0.53 – 1.12)	0.75 (0.52 – 1.08)	
	1 SDH	186/6	1.48 (0.58 – 3.83)	158/13	0.85 (0.48 – 1.50)	0.98 (0.61 – 1.57)	
	2 SDH	113/8	3.64 (1.54 – 8.60)	77/12	2.04 (1.14 – 3.67) *	2.45 (1.54 – 3.89) ***	
	≥ 3SDH	82/3	2.19 (0.63 – 7.58)	69/16	4.67 (2.78 – 7.84) ***	4.04 (2.51 – 6.51) ***	
e3e3	0 SDH	703/15	Ref	1845/181	Ref	Ref	
	1 SDH	878/25	1.32 (0.70 – 2.51)	859/97	1.32 (1.03 – 1.69) *	1.32 (1.05 – 1.66) *	
	2 SDH	527/21	2.31 (1.19 – 4.49) *	477/71	1.99 (1.51 – 2.63) ***	2.05 (1.59 – 2.63) ***	
	≥ 3SDH	301/20	4.84 (2.47 – 9.46) ***	375/77	3.40 (2.58 – 4.48) ***	3.63 (2.82 – 4.67) ***	
e4	0 SDH	319/7	1.09 (0.45 – 2.68)	762/91	1.43 (1.11 – 1.84) **	1.41 (1.10 – 1.79) **	
	1 SDH	401/11	1.57 (0.72 – 3.43)	368/48	1.68 (1.22 – 2.31) **	1.63 (1.22 – 2.19) **	
	2 SDH	231/8	1.84 (0.78 – 4.35)	240/45	2.94 (2.11 – 4.09) ***	2.67 (1.97 – 3.64) ***	
	≥ 3SDH	142/11	5.14 (2.36 – 11.22) ***	159/29	2.90 (1.93 – 4.34) ***	3.32 (2.34 – 4.72) ***	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Dementia defined according to

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S6.a Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile adjusting by the number of dementia risk factors.							
		ELSA		HRS		Fully adjusted Pooled analysis	I^2
APOE dosage	**N of SDH**	**N at risk / N event**	**HR (95%CI), p-value**	**N at risk / N event**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	
e2	**≤ 1 SDH**	168/2	Ref	403/37	Ref	Ref	
	2 SDH	186/8	3.59 (0.75 – 17.23)	158/18	1.30 (0.73 – 2.30)	1.50 (0.90 – 2.49)	0.0%
	3 SDH	113/8	7.02 (1.48 – 33.23) *	77/12	2.19 (1.13 – 4.22) *	2.65 (1.53 – 4.61) ***	
	≥ 4 SDH	82/4	4.90 (0.85 – 28.43)	69/16	3.96 (2.08 – 7.52) ***	3.59 (2.00 – 6.44) ***	
e3e3	**≤ 1 SDH**	173/8	Ref	1845/222	Ref	Ref	
	2 SDH	821/25	1.00 (0.60 – 1.65)	861/118	1.24 (0.99 – 1.55)	1.20 (0.98 – 1.47)	0.0%
	3 SDH	823/34	1.60 (0.93 – 2.73)	477/89	1.86 (1.44 – 2.40) ***	1.82 (1.45 – 2.28) ***	
	≥ 4 SDH	593/47	2.65 (1.50 – 4.68) ***	375/82	2.64 (2.02 – 3.46) ***	2.67 (2.09 – 3.40) ***	
e4	**≤ 1 SDH**	319/16	Ref	762/132	Ref	Ref	
	2 SDH	401/22	1.23 (0.64 – 2.37)	370/67	1.17 (0.87 – 1.58)	1.17 (0.90 – 1.53)	0.0%
	3 SDH	231/16	1.52 (0.76 – 3.06)	241/54	1.71 (1.23 – 2.36) **	1.64 (1.22 – 2.19) ***	
	≥ 4 SDH	142/15	2.62 (1.27 – 5.40) **	159/33	1.69 (1.12 – 2.54) *	1.88 (1.33 – 2.66) ***	
P for interaction			0.4859		0.00144	0.00102	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Dementia risk factors assessed: hypertension, diabetes, obesity, smoking, high-frequency drinking (drinking more than 5 days a week), physical inactivity (participating <1 time per week in moderate or vigorous physical activity), self-reported hearing problems, and depression (CES-D score >2 points).

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S6.b Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile adjusting by the number of dementia risk factors.							
		ELSA		HRS		Fully adjusted pooled analysis	I^2
APOE dosage	**N of SDH**	**N total / N events**	**HR (95%CI), p-value**	**N total / N events**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	0.0%
e2	**≤ 1 SDH**	168/2	0.30 (0.07 – 1.26)	403/37	0.71 (0.50 – 1.01)	0.66 (0.47 – 0.93) *	
	2 SDH	186/8	1.14 (0.52 – 2.51)	158/18	0.96 (0.60 – 1.56)	1.03 (0.69 – 1.55)	
	3 SDH	113/8	2.04 (0.92 – 4.48)	77/12	1.62 (0.91 – 2.90)	1.81 (1.14 – 2.85) *	
	≥ 4 SDH	82/4	1.39 (0.48 – 4.01)	69/16	3.21 (1.92 – 5.37) ***	2.67 (1.68 – 4.23) ***	
e3e3	**≤ 1 SDH**	173/8	Ref	1845/222	Ref	Ref	
	2 SDH	821/25	1.03 (0.62 – 1.69)	861/118	1.26 (1.01 – 1.58) *	1.23 (1.00 – 1.51) *	
	3 SDH	823/34	1.68 (0.98 – 2.86)	477/89	1.91 (1.49 – 2.45) ***	1.88 (1.50 – 2.35) ***	
	≥ 4 SDH	593/47	2.75 (1.56 – 4.83) **	375/82	2.75 (2.11 – 3.57) ***	2.79 (2.20 – 3.53) ***	
e4	**≤ 1 SDH**	319/16	1.36 (0.73 – 2.52)	762/132	1.73 (1.39 – 2.15) ***	1.70 (1.39 – 2.08) ***	
	2 SDH	401/22	1.63 (0.93 – 2.88)	370/67	1.96 (1.49 – 2.59) ***	1.91 (1.50 – 2.44) ***	
	3 SDH	231/16	2.00 (1.08 – 3.72) *	241/54	2.75 (2.03 – 3.71) ***	2.58 (1.97 – 3.37) ***	
	≥ 4 SDH	142/15	3.33 (1.76 – 6.30) ***	159/33	2.57 (1.76 – 3.75) ***	2.82 (2.05 – 3.88) ***	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Dementia risk factors assessed: hypertension, diabetes, obesity, smoking, high-frequency drinking (drinking more than 5 days a week), physical inactivity (participating <1 time per week in moderate or vigorous physical activity), self-reported hearing problems, and depression (CES-D score >2 points).

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S7 Table. Descriptive statistics of ELSA and HRS sample included and excluded based on complete social determinants of health information available at baseline						
	ELSA		P value	HRS		P value
	Included complete SDH (n: 4,330)	Excluded incomplete SDH (n: 1,201)		Included complete SDH (n: 7,530)	Excluded incomplete SDH (n: 11,386)	
Age Mean, SD (IQR)	67.98, 8.66 (61 – 74)	70.81, 10.63 (62 – 79)	$2.2e^{-16}$	65.00, 11.11 (56 – 73)	62.66, 10.94 (54 – 70)	$2.2e^{-16}$
Sex n (%)						
Male	2016 (46.6%)	473 (39.4%)	$9.765e^{-05}$	3152 (41.9%)	4802 (42.2%)	0.6671
Female	2314 (53.4%)	728 (60.6%)		4378 (58.1%)	6584 (57.8%)	
Race/ethnicity n (%)						
Non-Hispanic White	4229 (99.9%)	1201 (100%)	NA	6010 (79.9%)	8051 (70.9%)	$2.2e^{-16}$
Non-Hispanic Black	0	0		1082 (14.4%)	2303 (20.3%)	
Other (American Indian, Alaskan Native, Asian, and Pacific Islander)	1 (0.0%)	0		434 (5.8%)	997 (8.8%)	
Hispanic	0	0		686 (9.1%)	1705 (15.0%)	
Dementia risk factors n (%)						
Diabetes	413 (9.5%)	146 (12.2%)	0.007728	1365 (18.1%)	2116 (18.6%)	0.4275
Hypertension	1858 (42.9%)	580 (48.3%)	0.000885	3923 (52.1%)	5707 (50.1%)	0.00781
Obesity	1218 (31.0%)	297 (30.7%)	0.8593	2505 (33.7%)	3808 (34.1%)	0.6071
High-frequency drinking	772 (18.2%)	107 (14.4%)	0.01276	640 (8.5%)	832 (7.3%)	0.002927
No or little participation in physical activity	897 (20.7%)	414 (34.5%)	$2.2e^{-16}$	1873 (24.9%)	2966 (26.1%)	0.0694
Smoking	463 (10.7%)	143 (12.4%)	0.106	1083 (14.5%)	2068 (18.3%)	$7.888e^{-16}$
Hearing problems	184 (4.3%)	93 (7.8%)	$8.776e^{-07}$	323 (4.3%)	456 (4.0%)	0.3143
Depression	825 (19.1%)	288 (27.7%)	$8.597e^{-09}$	1561 (20.7%)	2751 (24.6%)	$5.568e^{-16}$
N of dementia risk factors n (%)						
0	921 (21.3%)	233 (19.4%)	$2.454e^{-08}$	1292 (17.2%)	1905 (16.7%)	0.02004
1	1445 (33.4%)	328 (27.3%)		2234 (29.7%)	3185 (28.0%)	
2	1062 (24.5%)	290 (24.1%)		1886 (25.0%)	2884 (25.3%)	
≥3	902 (20.8%)	350 (29.2%)		2118 (28.2%)	3412 (30.0%)	
Social determinants of health						
Education level n (%)						

Less than upper secondary	1336 (30.9%)	343 (45.6%)	$2.291e^{-14}$	1254 (16.7%)	2523 (22.2%)	$2.2e^{-16}$
Upper secondary and vocational	2217 (51.2%)	308 (40.9%)		4493 (59.7%)	6594 (57.9%)	
Tertiary	777 (17.9%)	102 (13.5%)		1783 (23.7%)	2267 (19.9%)	
Family income quartile by cohort n (%)						
<25th quartile income	979 (22.6%)	359 (30.5%)	$6.324e^{-14}$	1568 (20.8%)	2693 (23.7%)	$3.311e^{-08}$
25th – 75th quartile income	2224 (51.4%)	626 (53.2%)		3731 (49.5%)	5698 (50.0%)	
>75th quartile income	1127 (26.0%)	192 (16.3%)		2231 (29.6%)	2995 (26.3%)	
Healthcare access n (%)						
No private insurance	3760 (86.8%)	1075 (89.5%)	0.2047	2107 (28.0%)	3741 (33.1%)	$1.129e^{-13}$
Healthcare discrimination	186 (4.3%)	23 (3.4%)	0.2565	627 (8.3%)	55 (9.9%)	0.01347
Neighborhood environment n (%)						
Physical disorder						
Low	779 (18.0%)	221 (24.1%)	$1.174e^{-05}$	1864 (25.0%)	233 (32.7%)	$1.817e^{-05}$
Moderate	2116 (48.9%)	436 (48.0%)		3323 (44.5%)	298 (41.9%)	
High	1435 (33.1%)	252 (27.7%)		2276 (30.5%)	181 (18.1%)	
Social cohesion difficulties						
Low	1319 (30.5%)	295 (32.3%)	0.4912	1893 (25.3%)	244 (33.7%)	$1.16e^{-06}$
Moderate	2206 (50.9%)	457 (50.1%)		3365 (45.0%)	311 (43.0%)	
High	805 (18.6%)	160 (17.5%)		2214 (29.6%)	169 (23.3%)	
Social and community context n (%)						
Social support						
Low	1047 (24.2%)	302 (28.3%)	0.003525	1977 (26.3%)	211 (33.7%)	0.000188
Moderate	2335 (53.9%)	518 (48.5%)		3718 (49.4%)	289 (46.1%)	
High	1047 (24.2%)	302 (28.3%)		1835 (24.4%)	127 (20.3%)	
N of types of discrimination						
0	2409 (55.6%)	370 (54.7%)	0.355607	3036 (40.3%)	188 (33.8%)	0.005136
1	1264 (29.2%)	214 (31.6%)		2737 (36.3%)	235 (42.2%)	
≥2	657 (15.2%)	93 (13.7%)		1757 (23.3%)	134 (24.0%)	
APOE allele dosage						
e2e2	21 (0.5%)	6 (0.5%)	0.2269	46 (0.6%)	77 (0.7%)	0.1098

e2e3	561 (13.0%)	138 (11.5%)		895 (11.9%)	1431 (12.6%)	
e2e4	0 (0.0%)	0 (0.0%)		182 (2.4%)	276 (2.4%)	
e3e3	2574 (59.4%)	707 (58.9%)		4572 (60.7%)	6747 (59.3%)	
e3e4	985 (22.7%)	291 (24.2%)		1663 (22.1%)	2610 (22.9%)	
e4e4	189 (4.4%)	59 (4.9%)		172 (2.3%)	245 (2.2%)	
Overall APOE dosage						
e2 (e2e2, e2e3)	582 (13.4%)	144 (12.0%)	0.5284	941 (12.5%)	1508 (13.2%)	0.3692
e3e3	2574 (59.4%)	707 (58.9%)		4572 (60.7%)	6747 (59.3%)	
e4 (e2e4, e3e4, e4e4)	1174 (27.1%)	350 (29.1%)		2017 (26.8%)	3131 (27.5%)	
Any functional limitations in ADL n (%)	680 (15.7%)	345 (28.7%)	2.2e-16	14.7 (14.7%)	1800 (15.8%)	0.000511
Dementia n (%)	124 (2.9%)	141 (21.2%)	2.2e-16	164 (2.2%)	308 (3.0%)	0.03636

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; IQR: interquartile range; NA: not applicable.

*Excluding people 55 years or less.

<25^{th}: less than 25^{th} quartile by cohort; 25^{th} – 75^{th}: between 25^{th} and 75^{th} quartile by cohort; >75^{th}: more than 75^{th} quartile by cohort.

P-value for chi-square test (X^2) for nominal and ordinal variables and ANOVA test for continuous variables comparison.

S8.a Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile weighting by the inverse probability of being selected in the study.							
		ELSA		HRS		Fully adjusted Pooled analysis	I^2
APOE dosage	**N of SDH**	**N at risk / N event**	**HR (95%CI), p-value**	**N at risk / N event**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	
e2	**0 - 1 SDH**	163/0	Ref	395/36	Ref	Ref	
	2 SDH	185/8	3.42 (1.64 – 7.11) ***	154/16	1.28 (0.68 – 2.42)	1.65 (1.00 – 2.71) *	0.0%
	3 SDH	111/8	6.40 (2.99 – 13.71) ***	77/12	2.15 (1.03 – 4.50) *	2.92 (1.72 – 4.95) ***	
	≥ 4 SDH	79/3	4.07 (1.17 – 14.15) ***	69/16	4.42 (2.15 – 9.12) ***	4.42 (2.56 – 7.64) ***	
e3e3	**0 - 1 SDH**	693/27	Ref	1812/215	Ref	Ref	
	2 SDH	859/36	1.05 (0.64 – 1.72)	844/112	1.22 (0.97 – 1.54)	1.21 (0.99 – 1.49)	0.0%
	3 SDH	516/28	1.73 (1.02 – 2.93) *	467/88	2.05 (1.59 – 2.65) ***	2.01 (1.62 – 2.50) ***	
	≥ 4 SDH	297/22	3.17 (1.72 – 5.32) ***	372/82	3.59 (2.70 – 4.77) ***	3.55 (2.86 – 4.40) ***	
e4	**0 - 1 SDH**	315/16	Ref	752/130	Ref	Ref	
	2 SDH	394/22	1.36 (0.73 – 2.54)	362/65	1.08 (0.80 – 1.47)	1.13 (0.87 – 1.46)	0.0%
	3 SDH	223/15	1.51 (0.77 – 2.96)	237/54	2.01 (1.43 – 2.84) ***	1.88 (1.43 – 2.47) ***	
	≥ 4 SDH	140/14	2.97 (1.44 – 6.12) **	155/31	2.10 (1.31 – 3.39) **	2.25 (1.64 – 3.07) ***	
P for interaction			0.21807		0.0211	0.00075	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S8.b Table. Analysis of social adversity on the risk of dementia according to APOE allele risk profile weighting by the inverse probability of being selected in the study.							
		ELSA		HRS		Fully adjusted pooled analysis	I^2
APOE dosage	N of SDH	N total / N events	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	HR (95%CI), p-value	0.0%
e2	0 - 1 SDH	163/0	0.05 (0.00 – 0.08) ***	395/36	0.75 (0.52 – 1.08)	0.65 (0.47 – 0.91) *	
	2 SDH	185/8	1.18 (0.54 – 2.61)	154/16	1.00 (0.59 – 1.69)	1.10 (0.75 – 1.42)	
	3 SDH	111/8	2.11 (0.90 – 4.94)	77/12	1.70 (0.89 – 3.26)	1.93 (1.26 – 2.95) **	
	≥ 4 SDH	79/3	1.40 (0.41 – 4.76)	69/16	3.73 (2.11 – 6.59) ***	3.17 (2.08 – 4.83) ***	
e3e3	0 - 1 SDH	693/27	Ref	1812/215	Ref	Ref	
	2 SDH	859/36	1.08 (0.66 – 1.76)	844/112	1.23 (0.98 – 1.55)	1.23 (1.01 – 1.50) *	
	3 SDH	516/28	1.79 (1.06 – 3.03)	467/88	2.07 (1.60 – 2.67) ***	2.04 (1.65 – 2.53) ***	
	≥ 4 SDH	297/22	3.20 (1.82 – 5.64)	372/82	3.65 (2.73 – 4.86) ***	3.62 (2.94 – 4.46) ***	
e4	0 - 1 SDH	315/16	1.32 (0.72 – 2.41)	752/130	1.65 (1.33 – 2.06) ***	1.63 (1.34 – 1.99) ***	
	2 SDH	394/22	1.77 (1.03 – 3.06)	362/65	1.74 (1.30 – 2.32) ***	1.78 (1.40 – 2.26) ***	
	3 SDH	223/15	1.94 (1.06 – 3.54)	237/54	3.18 (2.26 – 4.47) ***	2.92 (2.27 – 3.75) ***	
	≥ 4 SDH	140/14	3.75 (1.93 – 7.28)	155/31	3.21 (1.98 – 5.20) ***	3.38 (2.54 – 4.50) ***	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.

Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I2: Random effect; Ref: reference value.
All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

S9.a Table. Analysis of social disadvantage on the risk of dementia according to APOE allele risk profile by sex.												
		Male				Male fully adjusted pooled analysis	Female				Female fully adjusted pooled analysis	I^2
		ELSA		HRS			ELSA		HRS			
APOE dosage	N of SDH	N total / N events	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	HR (95%CI), p-value	
e2	0 SDH	25/0	NA	156/16	Ref	Ref	15/0	NA	247/21	Ref	Ref	
	1 SDH	93/3	Ref	61/6	1.19 (0.46 – 3.06)	1.01 (0.44 – 2.35)	82/1	Ref	97/12	1.57 (0.76 – 3.25)	1.56 (0.77 – 3.18)	M: 0.0%
	2 SDH	91/5	1.60 (0.38 - .77)	31/4	1.83 (0.60 – 5.56)	1.51 (0.65 – 3.52)	91/4	3.72 (0.41 – 33.69)	46/8	2.87 (1.23 – 6.67) *	3.48 (1.63 – 7.44) **	F: 0.0%
	≥ 3SDH	60/6	3.87 (0.97 – 15.48)	31/4	1.64 (0.53 – 5.08)	2.40 (1.08 – 5.37) *	85/3	2.87 (0.28 – 29.03)	38/12	9.81 (4.43 – 21.72) ***	8.38 (3.87 – 18.17) ***	
e3e3	0 SDH	96/4	Ref	816/82	Ref	Ref	2/4	Ref	1029/140	Ref	Ref	
	1 SDH	418/14	0.90 (0.30 – 2.76)	374/45	1.47 (1.02 – 2.12) *	1.42 (1.01 – 2.00) *	77/4	0.51 (0.16 – 1.62)	487/73	1.56 (0.77 – 3.18)	1.20 (0.91 – 1.58)	M: 0.0%
	2 SDH	347/13	0.93 (0.30 – 2.87)	214/39	2.29 (1.55 – 3.37) ***	1.94 (1.34 – 2.79) ***	403/11	0.62 (0.21 – 1.82)	263/50	3.48 (1.63 – 7.44) **	1.81 (1.33 – 2.47) ***	F: 0.0%
	≥ 3SDH	257/22	2.94 (1.01 – 8.66) *	167/29	2.85 (1.84 – 4.42) ***	3.29 (2.27 – 4.78) ***	476/21	1.65 (0.57 – 4.74)	208/53	8.38 (3.87 – 18.17) ***	3.19 (2.35 – 4.34) ***	
e4	0 SDH	37/1	Ref	324/52	Ref	Ref	34/1	Ref	438/80	Ref	Ref	
	1 SDH	190/9	1.00 (0.12 – 7.95)	163/22	0.97 (0.59 – 1.59)	0.95 (0.60 – 1.50)	169/6	0.67 (0.07 – 5.73)	207/45	1.28 (0.88 – 1.86)	1.24 (0.86 – 1.78)	M: 0.0%
	2 SDH	179/16	2.13 (0.28 – 16.16)	90/20	1.82 (1.08 – 3.08) *	1.84 (1.16 – 2.93) *	227/12	1.11 (0.14 – 8.66)	151/34	1.83 (1.22 – 2.75) **	1.75 (1.19 – 2.58) **	F: 0.0%
	≥ 3SDH	111/11	2.53 (0.32 – 19.89)	67/13	2.14 (1.13 – 4.04) *	2.20 (1.29 – 3.75) **	146/13	2.05 (0.26 – 16.08)	92/20	1.64 (0.97 – 2.79)	2.01 (1.28 – 3.16) **	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.
All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$
Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.
Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S9.b Table. Analysis of social disadvantage on the risk of dementia according to APOE allele risk profile by sex.												
		Male				Male fully adjusted pooled analysis	Female				Female fully adjusted pooled analysis	I^2
		ELSA		HRS			ELSA		HRS			
APOE dosage	N of SDH	N total / N events	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	HR (95%CI), p-value	M: 5.5% F: 10.2%
e2	0 SDH	25/0	NA	156/16	0.97 (0.57 – 1.66)	0.93 (0.54 – 1.58)	15/0	0.0 (0.0 – 0.0)	247/21	0.61 (0.38 – 0.96) *	0.59 (0.38 – 0.94) *	
	1 SDH	93/3	0.74 (0.17 – 3.32)	61/6	1.15 (0.50 – 2.63)	1.07 (0.54 – 2.13)	82/1	0.18 (0.02 – 1.66)	97/12	0.93 (0.51 – 1.68)	0.84 (0.48 – 1.49)	
	2 SDH	91/5	1.24 (0.33 – 4.62)	31/4	1.50 (0.55 – 4.10)	1.58 (0.79 – 3.17)	91/4	0.70 (0.18 – 2.82)	46/8	1.70 (0.83 – 3.47)	1.71 (0.94 – 3.11)	
	≥ 3SDH	60/6	2.93 (0.82 – 10.41)	31/4	1.98 (0.72 – 5.44)	2.81 (1.44 – 5.46) **	85/3	0.55 (0.12 – 2.45)	38/12	5.64 (3.10 – 10.26) ***	3.69 (2.13 – 6.37) ***	
e3e3	0 SDH	96/4	Ref	816/82	Ref	Ref	2/4	Ref	1029/140	Ref	Ref	
	1 SDH	418/14	0.88 (0.30 – 2.79)	374/45	1.49 (1.03 – 2.15)	1.40 (1.00 – 1.96)	77/4	0.51 (0.16 – 1.60)	487/73	1.23 (0.93 – 1.64)	1.22 (0.93 – 1.60)	
	2 SDH	347/13	0.90 (0.30 – 2.79)	214/39	2.31 (1.57 – 3.39)	1.86 (1.31 – 2.66) ***	403/11	0.62 (0.21 – 1.81)	263/50	1.98 (1.43 – 2.75) ***	1.88 (1.40 – 2.53) ***	
	≥ 3SDH	257/22	2.86 (0.98 – 8.35)	167/29	2.90 (1.89 – 4.47)	3.22 (2.25 – 4.61) ***	476/21	1.62 (0.56 – 4.65)	208/53	3.13 (2.25 – 4.34) ***	3.32 (2.48 – 4.46) ***	
e4	0 SDH	37/1	1.12 (0.12 – 10.06)	324/52	1.78 (1.26 – 2.53)	1.76 (1.23 – 2.48) **	34/1	1.02 (0.11 – 9.21)	438/80	1.67 (1.26 – 2.19) ***	1.66 (1.26 – 2.18) ***	
	1 SDH	190/9	1.20 (0.37 – 3.91)	163/22	1.69 (1.05 – 2.71)	1.64 (1.08 – 2.49) *	169/6	0.59 (0.17 – 2.12)	207/45	2.07 (1.47 – 2.90) ***	1.97 (1.42 – 2.73) ***	
	2 SDH	179/16	2.50 (0.83 – 7.49)	90/20	3.05 (1.86 – 5.02)	3.09 (2.06 – 4.64) ***	227/12	1.02 (0.33 – 3.18)	151/34	2.95 (2.02 – 4.31) ***	2.78 (1.97 – 3.92) ***	
	≥ 3SDH	111/11	2.79 (0.88 – 8.80)	67/13	3.27 (1.80 – 5.95)	3.47 (2.17 – 5.53) ***	22/1	1.69 (0.55 – 5.19)	34/6	2.59 (2.02 – 4.31) ***	3.07 (2.06 – 4.56) ***	
P for interaction			0.852		0.110	0.150		0.912		0.003	0.004	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.
Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S10.a Table. Analysis of social disadvantage on the risk of dementia according to APOE allele risk profile by race.									
		Black people		White Caucasian people				White people adjusted pooled analysis	I^2
		HRS n: 668		ELSA n: 4,052		HRS n: 4,781			
APOE dosage	N of SDH	N total / N events	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	N total / N events	HR (95%CI), p-value	HR (95%CI), p-value	
e2	0 - 1 SDH	38/7	Ref	168/2	Ref	355/28	Ref	Ref	
	2 SDH	23/2	0.34 (0.07 – 1.74)	186/8	4.08 (0.86 – 19.34)	130/15	1.85 (0.98 – 3.47)	1.79 (0.99 – 3.25)	W: 0.0%
	3 SDH	17/3	1.19 (0.30 – 4.74)	113/8	7.48 (1.58 – 35.34) **	59/9	2.80 (1.31 – 5.98) **	3.18 (1.68 – 6.04) ***	
	≥ 4 SDH	26/6	2.10 (0.69 – 6.34)	82/4	6.37 (1.14 – 35.49) **	39/9	7.06 (3.19 – 15.61) ***	6.02 (3.07 – 11.83) ***	
e3e3	0 - 1 SDH	102/13	Ref	704/28	Ref	1697/205	Ref	Ref	
	2 SDH	103/23	1.66 (0.84 – 3.29)	878/36	1.06 (0.64 – 1.75)	712/89	1.29 (1.01 – 1.65) *	1.25 (0.99 – 1.57)	W: 0.0%
	3 SDH	78/26	3.09 (1.58 – 6.04) ***	527/28	1.79 (1.05 – 3.05) *	364/61	2.00 (1.50 – 2.66) ***	1.70 (1.31 – 2.21) ***	
	≥ 4 SDH	111/33	3.73 (1.96 – 711) ***	301/23	3.23 (1.85 – 5.66) ***	224/39	2.65 (1.88 – 3.74) ***	3.08 (2.35 – 4.05) ***	
e4	0 - 1 SDH	71/10	Ref	319/16	Ref	669/120	Ref	Ref	
	2 SDH	69/16	1.69 (0.76 – 3.76)	401/22	1.32 (0.69 – 2.52)	289/51	1.16 (0.83 – 1.61)	1.09 (0.80 – 1.48)	W: 0.0%
	3 SDH	66/13	2.15 (0.93 – 4.94)	231/16	1.58 (0.79 – 3.17)	164/37	1.73 (1.19 – 2.51) **	1.69 (1.21 – 2.35) **	
	≥ 4 SDH	62/18	2.59 (1.19 – 5.64) *	142/15	3.14 (1.55 – 6.40) ***	79/12	1.48 (0.81 – 2.68)	2.00 (1.33 – 3.01) ***	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$
All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.
Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.
Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S10.b Table. Analysis of social disadvantage on the risk of dementia according to APOE allele risk profile by race.									
		Black people		White people				White people adjusted pooled analysis	I^2
		HRS n: 766		ELSA n: 4,052		HRS n: 4,781			
APOE dosage	**N of SDH**	**N total / N events**	**HR (95%CI), p-value**	**N total / N events**	**HR (95%CI), p-value**	**N total / N events**	**HR (95%CI), p-value**	**HR (95%CI), p-value**	0.5%
e2	**0 - 1 SDH**	38/7	1.40 (0.56 – 3.52)	168/2	0.28 (0.07 – 1.18)	355/28	0.61 (0.41 – 0.90) *	0.59 (0.40 – 0.87) **	
	2 SDH	23/2	0.48 (0.43 – 2.11)	186/8	1.16 (0.53 – 2.56)	130/15	1.14 (0.67 – 1.92)	1.01 (0.63 – 1.62)	
	3 SDH	17/3	1.77 (0.50 – 6.21)	113/8	2.01 (0.91 – 4.43)	59/9	1.63 (0.83 – 3.17)	1.65 (1.01 – 2.68) *	
	≥ 4 SDH	26/6	3.45 (1.31 – 9.12) *	82/4	1.77 (0.62 – 5.07)	39/9	4.16 (2.13 – 8.14) ***	3.13 (1.91 – 5.13) ***	
e3e3	**0 - 1 SDH**	102/13	Ref	704/28	Ref	1697/205	Ref	Ref	
	2 SDH	103/23	1.68 (0.85 – 3.32)	878/36	1.08 (0.65 – 1.78)	712/89	1.28 (1.00 – 1.64)	1.26 (1.00 – 1.58)	
	3 SDH	78/26	3.13 (1.61 – 6.11) ***	527/28	1.85 (1.09 – 3.15) *	364/61	1.98 (1.49 – 2.64) ***	1.73 (1.35 – 2.23) ***	
	≥ 4 SDH	111/33	3.78 (1.98 – 7.19) ***	301/23	3.26 (1.87 – 5.71) ***	224/39	2.62 (1.86 – 3.69) ***	3.15 (2.42 – 4.10) ***	
e4	**0 - 1 SDH**	71/10	1.16 (0.51 – 2.65)	319/16	1.36 (0.73 – 2.52)	669/120	1.80 (1.44 – 2.26) ***	1.78 (1.43 – 2.23) ***	
	2 SDH	69/16	1.88 (0.90 – 3.91)	401/22	1.77 (1.01 – 3.11) *	289/51	2.09 (1.53 – 2.84) ***	1.92 (1.45 – 2.54) ***	
	3 SDH	66/13	2.40 (1.11 – 5.21) *	231/16	2.10 (1.13 – 3.90) **	164/37	3.10 (2.18 – 4.40) ***	2.96 (2.22 – 3.95) ***	
	≥ 4 SDH	62/18	2.97 (1.45 – 6.07) **	142/15	4.09 (2.17 – 7.71) ***	79/12	2.65 (1.48 – 4.76) ***	3.39 (2.35 – 4.90) ***	
P for interaction			0.186		0.740		0.006	0.005	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$
All models were adjusted by age, sex, and race. The pooled models were additionally adjusted by cohort.
Social adversity measured as N of unfavorable SDH exposed: Less than upper secondary education, being in the 25th lower family income range, 25th lower score in neighborhood physical disorder, 25th lower score in neighborhood social cohesion, having experienced poorer health service from a doctor or hospital, not having some private healthcare insurance, 25th lower score in perceived social support, having experienced two or more different types of discrimination.
Model properties: all the models' long-rank test p-value < 0.001. Fully adjusted model hazard proportionality assumption based on Schoenfeld residuals. The models meet the hazard proportionality assumption (p-value >0.05). All the variables meet the hazard proportionality assumption (p-value >0.05).

S11.a Table. Analysis of individual social determinants on the risk of dementia according to APOE allele risk profile by race.							
		Fully adjusted Pooled analysis for education level			Fully adjusted Pooled analysis for income level		I^2
APOE dosage	**Education level**	**N at risk / N event**	**HR (95%CI), p-value**	**Family income**	**N at risk / N event**	**HR (95%CI), p-value**	
e2	Tertiary education	259/1	Ref	High (>75th quartile)	314/3	Ref	
	Upper secondary and vocational	668/38	14.72 (2.02 – 107.47) **	Intermediate (25th to 75th quartile)	637/38	5.22 (1.60 – 17.01) **	0.0%
	Less than upper secondary school	282/34	34.56 (1.45 – 33.70) ***	Low (<25th quartile)	258/32	9.10 (2.70 – 30.60) ***	
e3e3	Tertiary education	1210/56	Ref	High (>75th quartile)	1419/52	Ref	
	Upper secondary and vocational	3180/226	1.56 (1.16 – 2.10) **	Intermediate (25th to 75th quartile)	3006/221	1.50 (1.11 – 2.04) **	0.0%
	Less than upper secondary school	1183/154	3.25 (2.37 – 4.45) ***	Low (<25th quartile)	1148/163	2.76 (1.99 – 3.84) ***	
e4	Tertiary education	588/46	Ref	High (>75th quartile)	632/34	Ref	
	Upper secondary and vocational	1380/130	1.21 (0.86 – 1.70)	Intermediate (25th to 75th quartile)	1332/148	1.54 (1.05 – 2.24) *	0.0%
	Less than upper secondary school	502/79	2.21 (1.50 – 3.24) ***	Low (<25th quartile)	506/73	2.01 (1.31 – 3.08) **	
P for interaction			<0.001			0.005	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.
All models were adjusted by age, sex, race, and cohort.
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

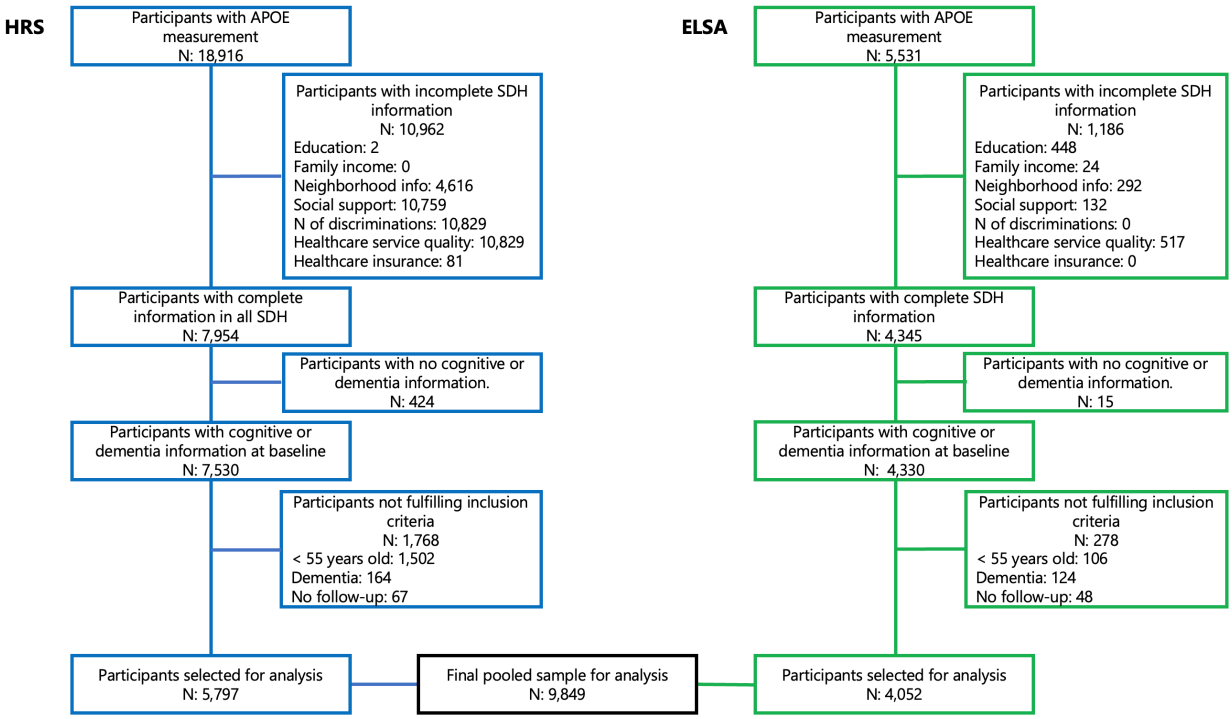
S11.b Table. Analysis of individual social determinants on the risk of dementia according to APOE allele risk profile by race.							
		Fully adjusted Pooled analysis for healthcare access and quality			Fully adjusted Pooled analysis for perceived social support		I^2
APOE dosage	**Healthcare access and quality**	**N at risk / N event**	**HR (95%CI), p-value**	**Perceived social support**	**N at risk / N event**	**HR (95%CI), p-value**	
e2	Adequate	537/29	Ref	High (>75th quartile)	331/21	Ref	
	Intermediate	639/42	1.59 (0.92 – 2.76)	Intermediate (25th to 75th quartile)	632/26	0.71 (0.40 – 1.29)	0.0%
	Low	33/2	1.40 (0.32 – 6.09)	Low (<25th quartile)	246/26	2.45 (1.35 – 4.42) **	
e3e3	Adequate	2488/184	Ref	High (>75th quartile)	1482/128	Ref	
	Intermediate	2908/222	1.59 (1.28 – 1.98) ***	Intermediate (25th to 75th quartile)	2901/205	1.03 (0.82 – 1.29)	0.0%
	Low	177/30	3.47 (2.32 – 5.17) ***	Low (<25th quartile)	1190/103	2.45 (1.35 – 4.42) ***	
e4	Adequate	1075/115	Ref	High (>75th quartile)	587/75	Ref	
	Intermediate	1306/129	1.49 (1.11 – 2.00) **	Intermediate (25th to 75th quartile)	1308/120	0.97 (0.72 – 1.30)	0.0%
	Low	71/11	2.45 (1.30 – 4.59) **	Low (<25th quartile)	575/60	1.34 (0.95 – 1.90)	
P for interaction			<0.001			0.012	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.
All models were adjusted by age, sex, race, and cohort.
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

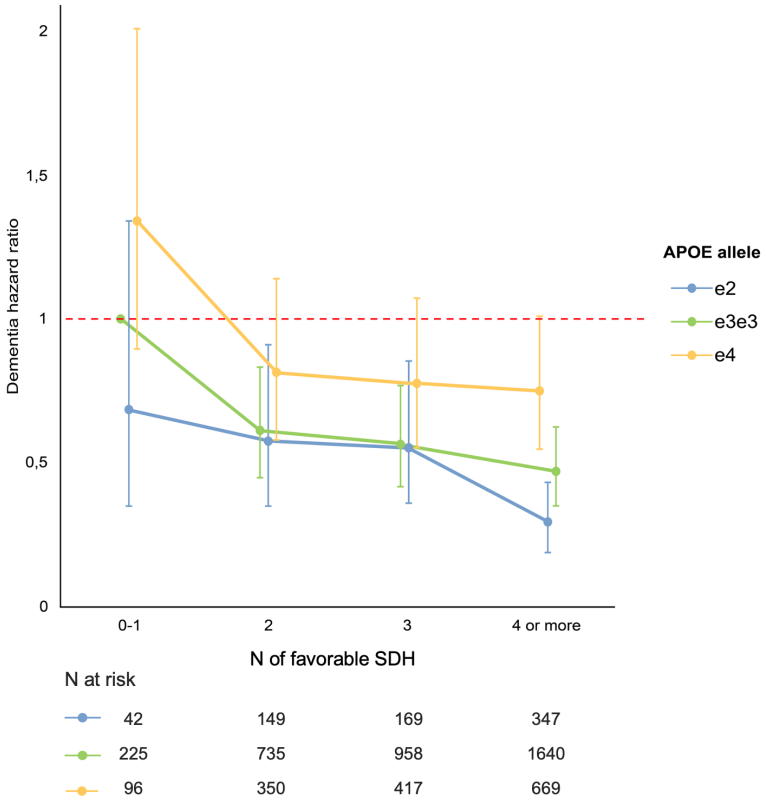
S11.c Table. Analysis of individual social determinants on the risk of dementia according to APOE allele risk profile by race.							
		Fully adjusted Pooled analysis for physical environment			Fully adjusted Pooled analysis for social cohesion		I^2
APOE dosage	**Neighborhood physical disorder**	**N at risk / N event**	**HR (95%CI), p-value**	**Neighborhood social cohesion**	**N at risk / N event**	**HR (95%CI), p-value**	
e2	Low (<25th quartile)	422/16	Ref	High (>75th quartile)	399/25	Ref	
	Intermediate (25th to 75th quartile)	562/32	1.62 (0.90 – 3.00)	Intermediate (25th to 75th quartile)	564/31	0.97 (0.57 – 1.66)	0.0%
	High (>75th quartile)	225/25	3.34 (1.76 – 6.33) ***	Low (<25th quartile)	246/17	1.51 (0.80 – 2.82)	
e3e3	Low (<25th quartile)	1846/127	Ref	High (>75th quartile)	1746/145	Ref	
	Intermediate (25th to 75th quartile)	2627/182	1.01 (0.81 – 1.27)	Intermediate (25th to 75th quartile)	2715/187	0.97 (0.78 – 1.20)	0.0%
	High (>75th quartile)	1100/127	1.71 (1.33 – 2.20) ***	Low (<25th quartile)	1112/104	1.52 (1.17 – 1.96) **	
e4	Low (<25th quartile)	775/69	Ref	High (>75th quartile)	749/83	Ref	
	Intermediate (25th to 75th quartile)	1172/121	1.18 (0.88 – 1.59)	Intermediate (25th to 75th quartile)	1182/115	1.19 (0.89 – 1.59)	0.0%
	High (>75th quartile)	523/65	1.24 (0.88 – 1.76)	Low (<25th quartile)	539/57	1.17 (0.83 – 1.64)	
P for interaction			0.533			0.934	

HRS: the Health and Retirement Study; ELSA: the English Longitudinal Study on Aging; SDH: Social Determinants of Health; HR: Hazard ratio; CI: Confidence Interval; I^2: Random effect; Ref: reference value.
All models were adjusted by age, sex, race, and cohort.
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

S1 Fig. Participant's study selection for HRS and ELSA populations.



S2 Fig. Social advantage Interacts with APOE Allele to Determine Risk of Developing Dementia.



The figure describes the dementia Hazard Ratio by APOE allele profile and number of favorable social determinants of health (SDH) exposure compared to people at intermediate genetic risk (APOE-e3e3) exposed at 0-1 unfavorable SDH. APOE-e2: e2e2, e2e3; APOE-e4: e2e4, e3e4, e4e4.