APOE ε4 and the influence of sex, age, vascular risk factors, and ethnicity on cognitive decline

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Abstract

We aimed to examine the relationship between *APOE*4* carriage on cognitive decline, and whether these associations were moderated by sex, baseline age, ethnicity, and vascular risk factors. Participants were 19,225 individuals aged 54-103 years from 15 longitudinal cohort studies with a mean follow up duration ranging between 1.2 and 10.7 years. Two-step individual participant data (IPD) meta-analysis was used to pool results of study-wise analyses predicting memory and general cognitive decline from carriage of one or two *APOE*4* alleles, and moderation of these associations by age, sex, vascular risk factors and ethnicity. Separate pooled estimates were calculated in both men and women who were younger (i.e., 62 years) and older (i.e., 80 years) at baseline. Results showed that *APOE*4* carriage was related to faster general cognitive decline in women, and faster memory decline in men. A stronger dose-dependent effect was observed in older men, with faster general cognitive and memory decline inthose carrying two versus one *APOE*4* allele. Vascular risk factors were related to an increased effect of *APOE*4* on memory decline in younger women, but a weaker effect of *APOE*4* on general cognitive decline in older men. The relationship between *APOE*4* carriage and memory decline was larger in older-aged Asians than Whites. In sum, *APOE*4* is related to cognitive decline in men and women, although these effects are enhanced by age and carriage of two *APOE*4* alleles in men, a higher numbers of vascular risk factors during the early stages of late adulthood in women, and Asian ethnicity.

Keywords: Cognitive decline, APOE genotype, epidemiology, sex, ethnicity

Introduction

Carriage of one or two Apolipoprotein E ε4 (*APOE*4*) alleles predicts prospective cognitive decline in nondemented older adults (1-10), and this effect increases with age (3, 11-14). Furthermore, compared to non-carriers, cognitive decline is faster in homozygous versus heterozygous *APOE*4* carriers (1, 6-9), implying that the effects of *APOE*4* on cognitive decline are dose-dependent. However, the nature and direction of sex differences in the relationship between *APOE*4* and cognitive decline are still unclear. For example, female *APOE*4* carriers displayed faster cognitive decline than male carriers in some studies (5, 15-18), but not all (18, 19). Furthermore, in other studies, larger effects of *APOE*4* homozygosity on cognitive dysfunction and decline were seen in men compared to women (16-19). Complicating things further, another study indicated that the effects of *APOE*4* on cognitive decline were larger in women than men, but only between the ages of 70-80 years,mplying that sex differences in the influenceof *APOE*4* on cognitive decline may be age-dependent (15). Because all *APOE*4* carriers were aggregated in this study, it is uncertain whether the observed age-dependent sex difference applied to both heterozygote and homozygote carriers. Given these mixed findings, the first aim of the present study was to determine if the relationship between *APOE*4* and cognitive decline was larger in women than men, if this difference occurred in both heterozygote and homozygote *APOE*4* carriers, and whether this was specific to certain age ranges.

The effects of vascular risk factors (e.g., atherosclerosis, diabetes, stroke) on cognitive decline are enhanced by carriage of *APOE*4* (20-23). Furthermore, age-related working memory deficits are mediated by increases in blood pressure in *APOE*4* carriers, but not in non-carriers(24). This implies that increasing numbers of vascular risk factors strengthen *APOE*4*'s effects on cognitive decline, and that such effects are compounded by increasing age, although this has yet to be formally tested. Hence, the second aim of the present study was to investigate whether increasing numbers of vascular risk factors exacerbated the effects of *APOE*4* on cognitive decline, and if increasing age further exacerbated these effects.

What also remains unclear is whether the effects of *APOE*4* on cognitive decline differ between ethnicities. In a large meta-analysis by Farrer et al. (25) the association between *APOE*4* and Alzheimer disease (AD) was weaker in African Americans and Hispanics, and stronger in Japanese individuals compared to Whites. Another meta-analysis, however, found that AD risk was lower among *APOE*4* carriers from Asia versus North America or Northern Europe (26). Important to note, however, is that the Asian participants pooled in this meta-analysis came from a broad range of Asian countries (including Russia, Iran, and Turkey) besides Japan. Because of this ethnic heterogeneity, it is difficult to draw definitive conclusionsregarding ethnic differences in the effects of *APOE*4* on cognitive decline. In light of these mixed findings, the third aim of the present study was to determine if the effects of *APOE*4* on cognitive decline, as well sex differences in these effects, differed between individuals of White and Asian ethnicity.

The Cohort Studies of Memory in an International Consortium (COSMIC) is a collaboration of members from around the world who share data from current or previous longitudinal population-based studies of ageing, with the aim of identifying factors that moderate the risk of dementia and cognitive decline (27). In the present study, harmonised data from 15 studies in COSMIC were pooled to examine the association between *APOE*4*and cognitive decline in late adulthood. Based on previous research, we firstly predicted that in both sexes, carriage of one or two *APOE*4* alleles would be related to faster cognitive decline, and that this effect would be worsened by older (baseline) age. Further, we predicted that these effects would be larger in women compared to men. Secondly, we predicted a dose-response effect, such that cognitive decline would be faster among carriers of two versus one *APOE*4* alleles, and that this effect would also worsen with older baseline age. We tentatively predicted that this dose response effect would be larger in men than women, although we anticipated both sexes to display a comparable worsening of this dose-response effect with increasing baseline age. Third, we hypothesized that the effects of *APOE*4* on cognitive decline, and the worsening of these effects with age, would be enhanced by increasing numbers of vascular risk factors. Finally, in light of the mixed evidence with regard to ethnicity, we did not have explicit hypotheses about whether the effects of *APOE*4* on cognitive decline would be stronger or weaker in Asian compared to White individuals.

Methods

We collected datasets from independent research studies participating in COSMIC. Studies are eligible to join COSMIC if they are longitudinal and population-based, evaluated cognition or dementia as a major objective, and recruited participants aged 60 years and above (28). This project was approved by the University of New South Wales Human Research Ethics Committee (HC 12446 and HC 17292). All cohorts contributing data to this study had prior ethics approval and all participants provided informed consent prior to participation (see Supplemental Information eTable1 for study-specific ethics approval details).

Study Selection

The 15 participating COSMIC studies provided individual participant data (IPD) as part of a broader research program to investigate risk and protective factors of cognitive ageing and dementia (28) (details about each study are provided in Supporting Information eTable2). Studies were included in this meta-analysis if the following IPD were available at baseline: age, sex, education, number of *APOE*4* alleles, data for four dementia risk factors (i.e., hypertension, diabetes, history of cardiovascular disease, history of stroke), score for a test of general cognition (typically the Mini Mental State Examination; MMSE), and dementia status. Criteria used to diagnose dementia as well as risk factor data available in each study are provided in Supporting Information eTable3. In terms of how *APOE*4* was measured, for the majority of studies, cell DNA was extracted from blood samples and/or buccal swabs, and the precise *APOE*4* genotype, including number of *APOE*4* alleles, was identified using polymerase chain reaction (PCR) amplification followed by restriction fragment length polymorphism analysis. Further details are provided in Supporting Information eTable4. Participants without the requisite data, or who had dementia at baseline were excluded from all analyses.

Cognitive assessment

Tests evaluating general mental status and verbal memory were the primary outcome measures as these were available in all studies. General cognition was evaluated using the Mini-Mental State Examination (MMSE)(29), which was administered in all but three studies. Two studies instead administered either the Modified MMSE (SALSA) or the Community Screening Instrument for Dementia (CHAS), scores for which were converted to MMSE scores using a published co-calibration table (30). EAS administered the Blessed Information Memory Concentration test, and a validated formula was used to convert these scores to MMSE scores (31). For the assessment of memory, we identified a single memory test that was maximally common across cohorts. This was a delayed word list recall test in ten studies, and the MMSE three-word recall sub-score for the remaining four studies which did not administer a specific memory test. The memory test used by each study is shown in Supporting Information eTable3. Both the tests of general cognition and memory were administered to participants once per wave.

Statistical Analysis

Standardisation of outcome measures

Within each study, raw MMSE and memory scores, pooled across all waves, were firstly transformed to have a Gaussian (or normal) distribution, calculated so that the transformed value had the same percentile value as the original value in the original distribution (in SPSS such scores are

described simply as normal scores, but are produced under the Rank Cases procedure). Outliers on these transformed scores were then winsorized to values plus or minus 3 standard deviations (SDs) from the mean scores. These transformed scores were then standardized by converting to *Z*-scores within each study, using estimated means and SDs of baseline scores within each study at common values of age, sex, and education. These common values were the average values at baseline from data pooled across all studies (common values: age = 72.7 years, education = 9.0 years, and sex = 0.42, indicating 42% males). SDs used for the calculation of these *Z*-scores were the estimated SDs of the residuals (i.e., the standard errors [SEs] of the estimates) obtained from the regression models for each study after adjustment for age, sex, and education. The purpose of such standardization was scale participants' scores, within each study, relative to a *standard* or *typical* older adult reference. This method of standardizing scores from multiple studies is essentially the same as that described by Griffith et al. (32) for obtaining standardized demographically based category-centered scores. However, instead of obtaining *Z*-scores using means and SDs from subsamples having the same restricted ranges of demographic characteristics, we used regression models to calculate estimated means and SDs for specific common values of demographic variables.

Longitudinal analyses

A two-step IPD meta-analysis was conducted to pool results across studies. Weighted generalized estimating equations (GEE) were used to analyse the relationship between *APOE*4* and cognitive decline, which incorporates Inverse Probability Weighting (IPW) to reduce bias in effect size estimates associated with attrition that is not completely random (33, 34). To obtain IPWs, logistic regression was used to regress a missing value indicator variable (1 = missing, 0 = not missing) for each outcome at each wave on participants' sex, baseline age, years of education, current data collection wave, presence of hypertension and diabetes, and their most recent outcome score. Predicted probabilities from each model were converted to stabilised IPWs and entered into the GEE analyses as a scale weight (35).

Multivariable GEE models were fit for each outcome measure in each study using an exchangeable correlation structure. The sandwich estimator was used as it ensures unbiased (i.e., robust) standard error estimates if the correlation structure has been mis-specified, especially when sample sizes are large (33, 34). The model included *APOE*4* group (carriers versus non-carriers), time in study, sex (treated categorically), age at baseline (centred at the mean of 72 years), all higher-order interactions between these variables, and the following covariates: education (centred at the mean of 9 years), hypertension, diabetes, history of cardiovascular disease, and history of stroke. We refit the above model comparing only homozygotesand heterozygotes to investigate the dose-dependence of *APOE*4* on cognitive decline. The main model term was the *APOE*4* x time interaction, which tested differences in the rate of cognitive decline between pairs of *APOE*4* groups (carriers versus non-carriers; homozygotes versus heterozygotes). The inclusion of interactions with sex (*APOE*4* x time x sex) and baseline age (*APOE*4* x time x age) enabled us to assess whether the association between *APOE*4* and cognitive decline differed between sexes and was related to baseline age. To explore significant interactions involving baseline age, we estimated effects at two distinct baseline ages: 62 years and 80 years, which were the mean of the bottom and top tertiles for baseline age, and represented "younger" and "older" elderly adults at baseline, respectively (36).

To examine whether vascular risk factors moderated the effects of *APOE*4* on cognitive decline, we computed a vascular risk index (VRISK), which was the sum of the following risk factors: hypertension, diabetes, history of cardiovascular disease, history of stroke, high cholesterol and current smoking (11), each of which coded as being present (1) or absent (0). A VRISK score was computed for participants with data for at least four risk factors. We repeated the above GEE analysis including VRISK (treated as numeric and continuous), *APOE*4*, time in study, age at baseline (centred at the mean), sex, and all interactions between these variables, controlling for education. The study-wise GEE analyses were fit in SPSS 23.0 (37). Regression coefficients for model terms were then pooled with random effects meta-analysis using the *metan* package in Stata 13 (38).

We next examined whether the relationship between *APOE*4* and cognitive decline, and its moderation by age, sex, and vascular risk factor history, differed between groups of white and Asian people. The white group included all individuals that were self-reported or classified as a white personfrom 8 cohorts of predominantly white people (CFAS, EAS, ESPRIT, HELIAD, Invece.Ab, LEILA, MoVIES, PATH, and Sydney MAS), and included in the Asian group were all individuals from 3 cohorts in countries with majority Asian populations (HK-MAPS, KLOSCAD, and SLASI, with the last cohort comprising 95.6% Chinese, 1.8% Malay, 2.1% Indian, and 0.6% other). Individuals from the Latin American and North American Hispanic cohorts (Bambui, CHAS, and SALSA) were not included in these groups. Each of the study-wise GEE models described above were re-fit, and metaregression was performed on model terms using the Stata *metareg* package, where ethnicity was treated as a binary, study-level variable (White = 0, Asian = 1). Significant interactions with ethnicity indicated that the term of interest (e.g., *APOE*4* x Time) differed between the two ethno-regional groups.

Data Availability Statement

Data used in this meta-analysis can be made available by request to p.sachdev@unsw.edu.au.

Results

Participant characteristics

Meta-analyses were performed on 19,225 participants spanning 15 studies, after excluding participants with dementia, or those lacking data for age, sex, education, baseline score for a test of general cognition or mental status, and baseline risk factors. Across studies, samples varied in size from 215 to 3517 participants. As shown in Table 1, the maximum number of assessment waves ranged from 2 to 16. The median number of assessment waves ranged between 1 and 12. The mean follow-up time ranged between 1.2 and 10.7 years across studies. Close to half the included studies had more than 4 assessment waves and a mean follow up time of more than 5 years. The maximum follow-up duration ranged from 4 to 19.6 years (see Supporting Information eTable5).

Baseline demographic characteristics of included participants are shown in Table 1, and baseline proportions of participants having each of the vascular risk factors is displayed in Supporting Information eTable6. In all but two studies, women outnumbered men. Mean years of education ranged between 2.8 years and 13.8 years, with an overall mean of 9 years. The majority of participants in each study were non-carriers (ranging from 73% to 86.7%). The proportion of participants that were heterozygote *APOE*4* carriers ranged between 11.4% to 25%, whereas the proportion of participants that were *APOE*4* homozygotes ranged between 0% to 2.1%. Across studies, the median VRISK score ranged between 1 and 2 risk factors.

Effect of *APOE*4* on cognitive decline

Table 2 displays the main effects of *APOE*4* status, indicating differences in baseline memory and MMSE performance between *APOE*4* carriers versus non-carriers, and between homozygotes and heterozygotes. The main effect of time is displayed capturing the annual change in MMSE and memory scores (i.e., cognitive decline) in non-carriers. The *APOE*4* x time interaction is displayed conveying/span> the increment in the annual rate of MMSE and memory decline for *APOE*4* carriers relative to non-carriers, and then in homozygotes relative to heterozygotes. The *APOE*4* xtime x age interaction reflects the amount by which group differences in cognitive decline (i.e., between *APOE*4* carriers versus non-carriers, andthen between homozygotes versus heterozygotes) increased or decreased per 1-year increase in age at baseline. Finally, the *P*-values for significance tests comparing sex differences on these model terms are displayed. Only model parameters pertinent to cognitive decline are discussed.

Women

In women overall, *APOE*4* carriers displayed significantly faster cognitive decline compared to non-carriers for the MMSE only (B = -0.026, SE = 0.008, P = 0.002) as indicated in Figure 1A. Although a dose-dependent *APOE*4* effect is implied by Figures 1A and 1B, this was non-significant for both measures. Furthermore, as indicated in Figures 1A and 1B, the effect of *APOE*4* on MMSE or memory decline was not significantly moderated by baseline age. This is reinforced by Figures 1C and 1D, which shows a comparable effect of *APOE*4* carriage, particularly carriage of two versus one *APOE*4* alleles, on faster MMSE and memory decline in younger and older females, respectively. Analyses within younger (i.e., 62 years) and older-aged (i.e., 80 years) women revealed no significant effects of *APOE*4* on MMSE (younger: B = -0.020, SE = 0.012, P = 0.080; older: B = -0.016, SE = 0.009, P = 0.061) or memory decline (younger: B = -0.012, SE = 0.011, P = 0.306; older: B = -0.021, SE = 0.014, P =0.150). Further, the dose-response effect of *APOE*4* was non-significant in both the younger (MMSE: B = 0.034, SE = 0.114, P = 0.769; Memory: B = -0.024, SE = 0.045, SE = 0.597) and older-aged women for both measures (MMSE: B = 0.137, SE = 0.100, P = 0.173; Memory: B = -0.084, SE = 0.045, P = 0.064).

Men

Figures 2A and 2B indicate a strong dose-dependent effect of *APOE*4* on memory and MMSE decline in men, particularly among older-aged males. In men overall, *APOE*4* carriers aggregated together had a significantly faster rate of memory decline than non-carriers (B = -0.018, SE = 0.007, P =0.013). This effect was dose-dependent (B = -0.062, SE = 0.029, P =0.032), implying that the overall effect of *APOE*4* in men was driven primarily by faster memory decline among the homozygotes. There were no significant interactions with baseline age, although results revealed that in older-aged men *APOE*4* carriage predicted faster memory (B = -0.040, SE = 0.015, P =0.007) and MMSE decline (B = -0.030, SE =

0.015, *P* =0.039), but not in younger-aged men (memory: *B* = -0.001, SE = 0.011, *P* = 0.980; MMSE: *B* = -0.008, SE = 0.008, *P* = 0.341). Furthermore, a significant dose-response effect emerged in older-aged men for both measures (memory: *B* = -0.181, SE = 0.059, *P* =0.002; MMSE: *B* = -0.179, SE = 0.070, *P* =0.011), but did not emerge in younger-aged men on either measure (Memory: *B* = *-0.028,* SE = 0.047, *P* = 0.553; MMSE: *B* = -0.066, SE = 0.080, *p* = 0.412). The fitted trajectories in Figures 2C and 2D show faster rates of decline among older versus younger *APOE*4* carriers, especially the homozygotes. Older baseline age worsened the dose-dependent effects of *APOE*4* on MMSE declinen men more than women (*B* =-0.020, SE = 0.006, *P* = 0.002). Furthermore, the dose-dependent effect of *APOE*4* on MMSE decline in older-aged participants was significantly larger in men than women (*B* = -0.226, SE = 0.106, *P* = 0.034).

Interaction between *APOE*4* carriage and Vascular Risk Factors

As shown in eTable7, a higher number of vascular risk factors was associated with a stronger *APOE*4* effect on memory decline in younger-agedwomen (*B* = -0.017, SE = 0.006, *P* =0.007). In contrast, a higher number of vascular risk factors was related to a weaker *APOE*4* effect MMSE decline in older men (*B* = 0.040, SE = 0.017, *P* =0.020).

Ethnoregional Differences

Complete results regarding ethnoregional differences in the association between *APOE**4 and cognitive decline are displayed in eTable8. Baseline age worsened the effects of *APOE*4* on memory decline in Asians (*B* = -0.011, SE = 0.005, *P* = 0.043), but not whites (*B* = 0.002, SE = 0.002, *P* =0.480), and this ethnic difference was significant (*B* = 0.013, SE = 0.005, *P* =0.037). Furthermore, as illustrated in Figure 3, in older-aged participants, *APOE*4* carriage had a stronger effect on memory decline in Asians than Whites (*B* = 0.127, SE = 0.046, *P* =0.023), and this effect wassignificant in Asians (*B* = -0.136, SE = 0.042, *P* =0.010) but not Whites (*B* = -0.009, SE = 0.019, *P* = 0.649). Subsequent analyses indicated that increasing numbers of vascular risk factors attenuated the effects of *APOE*4* on MMSE decline in Asians (*B* = 0.085, SE = 0.027, *P* = 0.010), but not Whites (*B* = 0.013, SE = 0.014, *P* = 0.388), and this ethnic group difference was significant (*B* = -0.072, SE = 0.031, *P* = 0.040).

Discussion

There was, overall, mixed support for our hypotheses, and we address each hypothesis in turn. Firstly, we predicted that overall, carriage of at least one *APOE*4* allele would be related to faster cognitive decline in both sexes, that these effects would be dependent on age, but emerge as being larger in women compared to men. Partially supporting this hypothesis, we found that *APOE*4* carriage was related to faster general cognitive decline in women, and faster memory decline in men – although in both sexes, particularly in men, this effect was primarily driven by carriage of two versus one *APOE*4* alleles. These findings broadly align with the body of research indicating that carriage of *APOE*4* predicts prospective cognitive decline (1-10). In contrast to our hypotheses, however, the effects of *APOE*4* carriage were not moderated by age at baseline in either sex. We did find, however, that in men but not women, *APOE*4* carriage was related to faster decline of general cognition and memory among those in the older-age range, although sex differences at this (or any other) age range did not emerge as significant. In general, prior cohort studies havereported mixed results in relation to whether the effects of *APOE*4* carriage on cognitive decline are larger in women than men. Our analysis, utilising a large and heterogeneous sample, however, suggests that carriage of *APOE*4* is related to cognitive decline to a comparable degree in both sexes.

Second, we hypothesised that the effects of *APOE*4* on cognitive decline would be dose-dependent and to a greater degree in men than women. Wealso predicted that this dose-dependent effect would increase with older baseline age, and comparably so in both sexes. Partially in line with this hypothesis, we found that carriage of two versus one *APOE*4* allele was associated with faster general cognitive and memory decline in men only, and specifically among those older in age (i.e., 80-years). Contrary to our predictions, however, we found that these dose-dependent *APOE*4* effectson decline of general cognition worsened with age in men more than women. Thus, our findings imply that the dose-dependent effects of *APOE*4*on cognitive decline, and the worsening of these effects with age, are stronger in men than women.

Studies have generally reported mixed findings as to whether the effects of *APOE*4* on cognitive decline do in fact worsen with age (11, 13, 39-41). These mixed results may be partially attributable to studies either pooling sexes and/or heterozygote and homozygote carriers together. Furthermore, whether such age-dependent effects of *APOE*4* on cognitive decline differ between sexes has for the most part not been tested in previous studies. By analysing sex, baseline age, and number of *APOE*4* alleles as separate variables in the present study, our study was able to

provide clarity regarding the complex interaction between *APOE*4*, sex, and age. Specifically, our findings suggest that the age-dependent effects of *APOE*4* on cognitive decline, specifically its dose-dependent effects, may be larger in men than women. This is in line with studies finding a stronger effect of *APOE*4* homozygosity on cognitive decline in men compared to women in the older age range (i.e., above 70 years of age). For example, Lehmann et al. (16) found that homozygous men, but not women with a mean age of 73 years were at greater risk of cognitive impairment relative to non-carriers. Similarly, Swan et al. found a stronger effect of *APOE*4* carriage on memory decline in men compared to women, whose mean ages were 75 and 71 years respectively (19). Mortensen et al.(15) in contrast, observed a stronger effect of *APOE*4* carriage on cognitive decline in women than men, specifically between the ages of 70 and 80 years. These findings, which are contrary to ours, imply that the effects of *APOE*4* on cognitive decline are exacerbated by age to a greater degree in women than men. However, it should be noted that Mortensen et al. (15) administered tests that evaluated executive functions and processing speed. This suggests that *APOE*4*-mediated cognitive decline may indeed worsen with age to a greater extent in women than men, but in relation to executive functions and processing speed abilities specifically. In line with these results, Reinvang et al. (17) found that *APOE*4* homozygosity was associated with impaired working memory performance in men and not women with a mean age of 65 years, suggesting that the decline of executive abilities occurs earlier in men than women.

Taken together, sex differences in the effects of *APOE*4* on cognitive decline, and how these effects are exacerbated by older age may also be dependent on the cognitive ability being evaluated. Our findings suggest that in relation to verbal memory specifically (i.e., the cognitive ability measured by the MMSE and memory tests admnistered in the present study (42)), there is a larger age-related worsening of cognitive decline associated with carriage of two versus one *APOE*4* allele in men than women. Evidence indicates that women have a lifelong advantage over men with regard to verbal memory abilities (43), with more advanced neuropathology needed to detect significant verbal memory deficits in women compared to men. Because of this lifelong advantage, male *APOE*4* carriers may evidence larger verbal memory decline with increasing age than female carriers, as indicated by our findings. The mechanisms underlying this gender difference are unclear. Studies indicate smaller hippocampal volume in *APOE*4* homozygous men than women, suggesting that male *APOE*4* carriers may experience more rapid age-related hippocampal atrophy, leading to faster verbal memory decline than women (21). Furthermore, given that testosterone has neuroprotective effects (e.g., reduction of Aβ secretions in cell cultures and phosphorylation of tau proteins (18)), decreasing levels of testosterone in the ageing male may progressively worsen *APOE*4*-related neurodegeneration over time (21), leading to *APOE*4*-mediated verbal memory decline that worsens with age to a greater extent in men than women. Further research is needed to pinpoint the precise mechanisms underlying the stronger age-dependent effects of *APOE*4*on verbal memory decline in men versus women.

For our third hypothesis, we predicted that the relationship between *APOE*4* and cognitive decline would be compounded by increasing numbers of vascular risk factors. We found partial support for this hypothesis, as our results indicated the combined effects of *APOE*4* and vascular history on cognitive decline were moderated by sex andaseline age. Specifically, increasing numbers of vascular risk factors were related to a stronger *APOE*4*effect on memory decline in younger-aged women only. It is known that *APOE*4* and vascular risk factors combine synergistically to induceneurovascular damage and adverse white matter changes that lead to a compounded risk of cognitive decline and AD (20-22, 24, 44). The fact that significant results were limited to younger women could be because men and women at this age range differed in the extent to which their vascular risk factors were treated (45) or in the combination of risk factors that contributed to their VRISK scores. Results in Supporting Information eTable9, however, indicate that a similar proportion of the younger men and women with VRISK scores above 3 had each of the risk factors. Alternatively, our results may indicate a survival bias, given that men do not live as long as women with heart disease (46). Furthermore, among men, *APOE*4*carriage has been found to predict death associated with coronary heart disease and stroke (47, 48). A survival bias would leave resilient male participants whose cognition would be relatively unimpaired by their vascular risk factor profile irrespective of whether or not they were *APOE*4*carriers. Hence this may explain why vascular risk factors did not moderate the effects of *APOE*4* on cognitive decline in the younger aged men.

Interestingly, we found that higher vascular risk factors were related to an *attenuated APOE*4* effect on general cognitive decline in older participants, with the effect being significant in older men. This aligns with numerous other studies showing that vascular risk factors (e.g., obesity, hypertension, high cholesterol) in later life are related to reduced dementia risk (49-51). These results are again consistent with a survival bias mechanism, as *APOE*4* carriers (particularly males (47, 48)) with multiple vascular risk factors would have likely passed away before

80 (the older age point in our study). Presumably then, the surviving male *APOE*4* carriers at the older age ranges (i.e., 80+) would be even more resilient and cognitively intact than those in the younger age ranges (i.e., 60+) – hence leading to an attenuated interaction between *APOE*4* and vascular risk factors on cognitive decline among men in the old age range only.

The third and final aim of the present study was to clarify whether there were ethnic differences in the effects of *APOE*4* on cognitive decline. Because the results of previous studies were mixed, we did not have explicit hypotheses regarding whether the effects of *APOE*4* on cognitive decline would be stronger or weaker in Asian compared to White individuals. Our results implied the existence of ethnic differences but at specific ages. Specifically, in older-aged participants, *APOE*4* had a stronger effect on memory decline in Asians versus Whites. Similarly, Farrer et al. (25), found that AD risk was elevated in Japanese versus White *APOE*4* carriers. Crean et al. (26), however, found that Asian *APOE*4* carriers had a lower risk of AD than *APOE*4* carriers from North America or Northern Europe, although the Asian group in this study was quite heterogeneous, as it included participants from countries not typically classified as Asian (e.g., Russia, Iran). The ethnic differences we observed are unlikely due to higher vascular risk burden in Asians than Whites given that vascular risk factors did not moderate the effect of *APOE*4* on memory decline in either ethnicity; and increasing number of vascular risk factors *weakened* the effect of *APOE*4* on MMSE decline in Asians and not Whites.Importantly, though, we did not have data on midlife vascular risk factors which are known to be related to more severe cognitive deficits than in latelife (52). It is possible that Asians – who are more susceptible to midlife vascular risk factors at "normal" BMI values than White (53, 54), displayed faster memory decline because of more extensive neuropathology caused by interactions between *APOE*4* and vascular risk factorsexperienced in midlife (49, 55). The veracity of this explanation cannot be deduced from our study, thus further research examining the mechanisms mediating ethnoregional differences in vulnerability to *APOE*4* is needed.

Strengths and Limitations

Strengths of our study include the large sample size and availability of IPD, enabling us to explore the influence of age, sex, ethnicity, and vascular risk factors on both the overall and dose-dependent effects of *APOE*4* on cognitive decline. We also controlled for numerous AD risk factors which has not been performed consistently in previous meta-analyses, strengthening the internal validity of our conclusions. Furthermore, pooling data from 15 population-based studies from 11 countries spread across 5 continents enhances our ability to generalise findings across non-White populations. In terms of limitations, data were limited to the number of *APOE*4* alleles participants carried as opposed to their entire APOE genotype. Hence, comparisons could not be made between individuals with specific pairs of APOE alleles. Second, data limitations also precluded us from examining whether the contrasting effects of vascular risk factors we observed in younger versus older *APOE*4* carriers were due todifferential treatment of vascular risk factors between these age groups. Third, ethnoregional comparisons were limited to Whites and Asians due to the smaller number of participants in other ethnic groups. Finally, only decline on tests of memory and the MMSE was examined (both of which arehighly verbal measures), precluding us from generalising our conclusions to other cognitive domains.

Conclusions

Although there is overwhelming evidence that carriage of *APOE*4* is related to faster cognitive decline in late adulthood, there is less clarity regarding how this relationship is moderated by age, sex, ethnicity, and the presence of vascular risk factors. Utilising pooled data from 15 international longitudinal cohort studies, we were equipped with sufficient power to address these moderating factors, and given the diversity of the pooled studies, our results have the potential to generalise to a global scale. Overall, our results indicated a complex interaction between number of *APOE*4* alleles, age at baseline, sex, ethnicity, and current vascular history on the relationship between *APOE*4* and cognitive declie in old age. Namely, we found that *APOE*4* carriage was related to faster decline of general cognitive abilities in women, and faster memory decline in men. Older baseline age worsened the dose-dependent effect of *APOE*4* on general cognitive decline to a stronger degree in men than women. This dose-response effect only emerged in older-aged men. Vascular risk factors worsened the effects the *APOE*4* on cognitive decline in younger women, but attenuated effects of *APOE*4* on cognitive decline in older men. Finally, *APOE*4* carriage was more detrimental to memory decline in older-aged Asians than Whites. Data limitations prevent us from being able to generalise these conclusions across all cognitive domains, *APOE*4* genotypes, and to vascular risk factors experienced in midlife, and so these remain fruitful areas for future investigations. Treatment of vascular risk factors, alone, or in combination with preventive care (e.g., diet, exercise, intellectual and social stimulation), and APOE-targeted pharmacological interventions could be initiated early to minimise or prevent cognitive decline associated with carriage of *APOE*4*.

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Conflicts of Interest

Richard B. Lipton Is the Edwin S. Lowe Professor of Neurology at the Albert Einstein College of Medicine in New York. He receives research support from the NIH: 2PO1 AG003949 (mPI), 5U10 NS077308 (PI), RO1 NS082432 (Investigator), 1RF1 AG057531 (Site PI), RF1 AG054548 (Investigator), 1RO1 AG048642 (Investigator), R56 AG057548 (Investigator), K23 NS09610 (Mentor), K23AG049466 (Mentor), 1K01AG054700 (Mentor). He also receives support from the Migraine Research Foundation and the National Headache Foundation. He serves on the editorial board of Neurology, senior advisor to Headache, and associate editor to Cephalalgia. He has reviewed for the NIA and NINDS, holds stock options in eNeura Therapeutics and Biohaven Holdings; serves as consultant, advisory board member, or has received honoraria from: American Academy of Neurology, Alder, Allergan, American Headache Society, Amgen, Autonomic Technologies, Avanir, Biohaven, Biovision, Boston Scientific, Dr. Reddy's, Electrocore, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Merck, Pernix, Pfizer, Supernus, Teva, Trigemina, Vector, Vedanta. He receives royalties from Wolff's Headache 7th and 8th Edition, Oxford Press University, 2009, Wiley and Informa. Henry Brodaty is on the Advisory Committee for Nutricia Australia; Clinincal Advisory Committee, Montefiore Home; Medical Advisory Committee, Cranbrook Care. Nikolaos Scarmeas reports personal fees from Merck Consmer Health and the NIH outside the submitted work. Mary Ganguli was on Biogen Inc.'s "Patient Journey Advisory Group" in 2016 and 2017. Allison E. Aiello is a consultant for Kinsa Inc. and has received an unrestricted gift from Gojo Inc. Henry Brodaty is on the Advisory Board of Nutricia Australia.

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Captions for Tables and Illustrations

Tables

Table 1. Descriptive Statistics of Each Included Study at Baseline

Table 2. Results of IPD Meta-Analysis Examining the Association Between *APOE*4* and Cognitive Decline

Figure Legends

Figure 1. Association between *APOE*4* and cognitive decline in women

(A) Mean annual rates of change in MMSE performance and standard errors for women aged 62 years (younger) and 80 years (older) at baseline in each of the *APOE*4* groups. (B) Mean annual rates of change in memory performance and standard errors for women aged 62 years (younger) and 80 years (older) at baseline in each of the *APOE*4* groups. (C) Fitted trajectories plotting changes in MMSE performance over time in 62-year old (younger) and 80-year old (older) women in each of the *APOE*4* groups. (D) Fitted trajectories plotting changes in memory performance over time in 62-year old (younger) and 80-year old (older) women in each of the *APOE*4* groups. NC = Non-carrier; C = Carrier.

Figure 2. Association between *APOE*4* and cognitive decline in men

(A) Mean annual rates of change in MMSE performance and standard errors for men aged 62 years (younger) and 80 years (older) at baseline in each of the *APOE*4* groups. (B) Mean annual rates of change in memory performance and standard errors for men aged 62 years (younger) and 80 years (older) at baseline in each of the *APOE*4* groups. (C) Fitted trajectories plotting changes in MMSE performance over time in 62-year old (younger) and 80-year old (older) males in each of the *APOE*4* groups. (D) Fitted trajectories plotting changes in memory performance over time in 62-year old (younger) and 80-year old (older) males in each of the APOE*groups. (E) Fitted trajectories plotting changes in MMSE scores in 80-year old (older) male and female heterozygotes and homozygotes.

Figure 3. Effects of *APOE*4* on cognitive decline in Asian and White men

(A) Fitted trajectories plotting changes in memory performance over time in 62-year old (younger) and 80-year old (older) Asian *APOE*4* carriers and non-carriers. (B) Fitted trajectories plotting changes in memory performance over time in 62-year old (younger) and 80-year old (older) White *APOE*4* carriers and non-carriers. NC = Non-carrier, C = Carrier.

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Tables

Table 1. Descriptive Statistics of Each Included Study at Baseline

		Number of Waves	**Time in study**	**Female**	**Age, y**	**Education, y**	**Baseline cognition (Z-score)**			***APOE*4* group[a]**		
							MMSE	**Memory**	**VRISK**	**NC**	**HET**	**HOM**
	N	**Median (IQR)**	**M (SD)**	**%**	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**	**Median (IQR)**	**%**	**%**	**%**
Bambui	1313	12 (7-16)	9.7 (5.0)	61.5	68.7 (6.9)	2.8 (3)	-1.02 (1.2)	-0.01 (1)	2 (1-2)	74.9	23.2	1.8
CFAS	1957	2 (2-3)	3.3 (4.0)	64.9	74.3 (6.6)	9.7 (1.8)	-0.04 (1.1)	-0.01 (1.1)	2 (1-3)	76.3	21.9	1.8
CHAS	977	2 (1-2)	5.5 (2.2)	60.1	74.1 (6.6)	9.4 (4.7)	-0.25 (1.1)	-0.12 (1)	1 (0-1)	84	14.9	1.1
EAS	873	4 (2-7)	4.4 (3.9)	59.7	78 (5.3)	13.2 (3.5)	0.49 (1.1)	-0.16 (1.1)	1 (1-2)	77.3	21	1.7
ESPRIT	2118	4 (3-4)	5.4 (2.8)	58.3	73 (5.5)	10.3 (3.8)	0.08 (1.1)	0.01 (1)	2 (1-2)	80.6	18.6	0.8
HELIAD	901	1 (1-2)	1.2 (1.5)	55.1	72.9 (5.7)	6.6 (3.8)	-0.22 (1.1)	-0.23 (1.1)	2 (1-2)	83.2	16.1	0.7
HK-MAPS	255	3 (2-3)	3.7 (2.4)	47.6	70.6 (6.4)	5.5 (4.6)	-0.24 (1.2)	-0.15 (1.1)	1 (0-2)	86.7	11.4	2
Invece.Ab	1210	2 (2-2)	1.8 (0.8)	53.3	72.2 (1.3)	6.9 (3.3)	-0.16 (1.1)	-0.07 (1)	1 (1-2)	81.9	17.8	0.3
KLOSCAD	3517	2 (2-2)	1.7 (0.9)	55.5	69.1 (6.3)	8.5 (5.2)	-0.06 (1.2)	0.22 (1.1)	2 (1-2)	75.3	24.1	0.6
LEILA	243	6 (4-6)	7.3 (3.0)	79.8	80.5 (4.2)	11.9 (1.8)	0.08 (1.1)	0.06 (1.1)	1 (1-2)	84	16	0
MoVIES	215	6 (5-7)	10.7 (2.5)	51.6	73.4 (5.6)	10.5 (2.5)	0.09 (1)	-0.1 (1.1)	1 (1-2)	74.9	23.3	1.9

PATH	2367	3 (3-3)	6.7 (2.7)	48.4	62.5 (1.5)	13.8 (2.7)	0.9 (1)	0.63 (1)	1 (1-2)	73	25	2.1
SALSA	1538	6 (4-7)	5.7 (3.0)	58.6	70.1 (6.7)	7.5 (5.3)	-0.09 (1.2)	0.05 (1.2)	2 (1-3)	86.7	12.5	0.7
SLASI	788	2 (1-3)	2.0 (1.7)	61	64.6 (6.8)	7 (4.5)	0.05 (1.2)	0.18 (1.1)	1 (1-2)	84.1	15.2	0.6
Sydney MAS	953	4 (3-4)	4.7 (2.0)	54.6	78.7 (4.8)	11.6 (3.5)	-0.08 (1.1)	-0.28 (1.1)	2 (1-3)	77.3	21	1.7

Abbreviations: *APOE*4* = Apolipoprotein E □4, Bambui = Bambui Cohort Study of Aging, CHAS = Cuban Health and Alzheimer Study, EAS = Einstein Aging Study, ESPRIT = Etude Santé Psychologique et Traitement, HELIAD = Hellenic Longitudinal Investigation of Aging and Diet, HET = *APOE*4* heterozygote, HK-MAPS = Hong Kong Memory and Ageing Prospective Study, HOM = *APOE*4* Homozygote, Invece.Ab = Invecchiamento Cerebrale in Abbiategrasso, IQR = interquartile range, KLOSCAD = Korean Longitudinal Study on Cognitive Aging and Dementia, M = mean, MoVIES = Monongahela Valley Independent Elders Survey, NC = *APOE*4* Non-carrier, PATH = Personality and Total Health Through Life Project, SALSA = Sacramento Area Latino Study on Aging, SD = standard deviation, SGS = Sasaguri Genkimon Study, SLASI = Singapore Longitudinal Ageing Studies, SydneyMAS = Sydney Memory and Ageing Study, VRISK = Vascular risk factor index score, ZARADEM*P* =Zaragoza Dementia Depression Project.

[a] Values in percentages are in relation to the included sample of the study displayed in the column labelled *N*. Percentages may sum to less or more than 100 due to rounding error.

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Table 2. Results of IPD Meta-Analysis Examining the Association Between *APOE*4* and Cognitive Decline

	Female		Male		P for sex difference [g]
	B	CI	B	CI	
MMSE					
*APOE*4* [b]					
Carrier v non-carrier [d]	0.013	(-0.07, 0.096)	-0.012	(-0.108, 0.084)	0.660 [h]
Homozygotes versus heterozygotes [e]	0.003	(-0.340, 0.3453)	0.077	(-0.457, 0.61)	0.329
Time [c]	-0.021	(-0.06, 0.018)	-0.031	(-0.06, -0.002)*	0.021 [i]
APOE*4 x Time					
Carrier v non-carrier [d]	-0.026	(-0.042, -0.01)**	-0.014	(-0.033, 0.005)	0.74 [j]
Homozygotes versus heterozygotes [e]	0.088	(-0.071, 0.246)	-0.078	(-0.171, 0.014)	0.709 [j]
APOE*4 x Time x Age [f]					
Carrier v non-carrier	0.0005	(-0.002, 0.003)	-0.001	(-0.003, 0.001)	0.238 [k]
Homozygotes versus heterozygotes	0.006	(-0.004, 0.017)	0.02	(-0.009, 0.05)	0.259 [k]
Memory					
*APOE*4* [b]					
	-0.078	(-0.145, -0.011)*	-0.063	(-0.126, -0.001)*	0.885
	-0.351	(-0.676, -0.026)*	-0.003	(-0.316, 0.311)	0.488

Time [c]	-0.044	(-0.078, -0.009)*	-0.028	(-0.06, 0.004)	0.812
APOE*4 x Time					
Carrier v non-carrier [d]	-0.014	(-0.03, 0.002)	-0.018	(-0.033, -0.004)*	0.374
Homozygotes versus heterozygotes [e]	-0.043	(-0.106, 0.02)	-0.062	(-0.119, -0.005)*	0.356
APOE*4 x Time x Age [f]					
Carrier v non-carrier	-0.078	(-0.145, -0.011)*	-0.063	(-0.126, -0.001)*	0.848
Homozygotes versus heterozygotes	-0.044	(-0.078, -0.009)*	-0.028	(-0.06, 0.004)	0.002

Abbreviations: *APOE*4* = Apolipoprotein E □4, MMSE = Mini Mental State Examination

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[a] Values come from multivariate GEE models including the following terms APOE group, time in study, age at baseline (centered at the mean baseline age of 72), sex, all interactions among these variables, and the following covariates: education (centred at the mean of 9 years), hypertension, diabetes, history of cardiovascular disease, and history of stroke. Terms relating to the effect of *APOE*4* on baseline cognition are not discussed.

[b] Values reflect the mean difference in baseline scores firstly for APOE*4 carriers versus non-carriers, and then for homozygotes versus heterozygotes on the specified outcome measure. Negative values indicate lower mean baseline scores for carriers relative to non-carriers, or lower mean baseline scores for homozygotes versus heterozygotes.

[c] Values reflect the annual rate of decline in non-carriers on the specified outcome measure, where negative values indicate the average rate of decrease in cognitive scores per year.

[d] Values reflect *B*-coefficients for the *APOE*4* group x time interaction term comparing non-carriers to carriers. Negative *B*-values indicate a faster rate of cognitive decline on the specified outcome measure in *APOE*4* carriers, or in homozygotes compared to heteozygotes.

[e] Values reflect *B*-coefficients for the *APOE*4* group x time interaction term comparing homozygotes to heterozygotes. Negative *B*-values indicate a faster rate of cognitive decline on the specified outcome measure in homozygotes compared to heterozygotes. These estimates were obtained from arefitted multivariable GEE model where the comparison between carriers and non-carriers was replaced with the comparison between heterozygotes and homozygotes.

[f] Values reflect *B*-coefficients for the *APOE*4* group x time x baseline age interaction term, with age entered at the mean baseline age of 72 years. Negative *B*-values for the effect of age indicate that if *APOE*4* (or carriage of two versus one *APOE*4* alleles) is related to faster decline, this rate of decline increases with every 1-year increase in age at baseline.

[g] Values reflect the *P*-values from significance tests of terms comparing the size of the specified model term between men and women, i.e., terms involving interactions with sex.

[h] *P*-value from the significance test of the *APOE*4* x sex term, comparing differences between men and women in the effect of *APOE*4* carriage on cognition at baseline.

[i] *P*-value from the significance test of the *APOE*4* x time term, comparing differences between men and women in rate of cognitive decline, per year, among non-carriers.

[j] *P*-value from the significance test of the *APOE*4* x time x sex term, comparing the difference between men and women in the effect of *APOE*4* carriage on cognitive decline (firstly between *APOE*4* carriers versus non-carriers, then between homozygotes versus heterozygotes)span style="font-family:'Times New Roman'">.

[k] *P*-value from the significance test of the *APOE*4* x time x baseline age x sex term, comparing the difference between in the effect of older baseline age on *APOE*4*-related cognitive decline (firstly between *APOE*4* carriers versus non-carriers, then between homozygotes versus heterozygotes).

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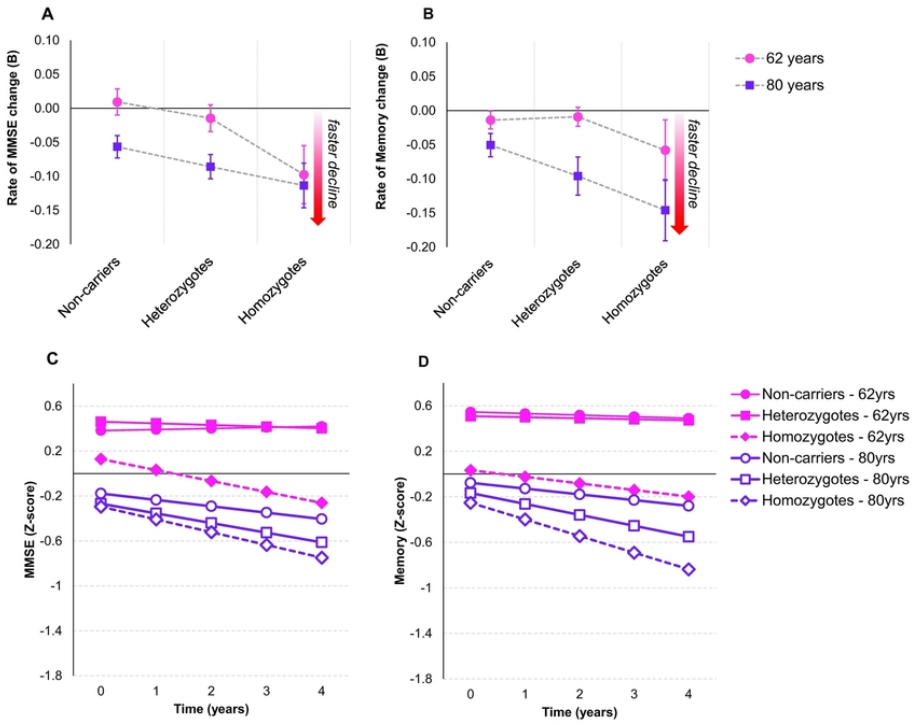

Figure 1. Association between APOE*4 and cognitive decline in women
(A) Mean annual rates of change in MMSE performance and standard errors for women aged 62 years (younger) and 80 years (older) at baseline in each of the APOE*4 groups. (B) Mean annual rates of change in memory performance and standard errors for women aged 62 years (younger) and 80 years (older) at baseline in each of the APOE*4 groups. (C) Fitted trajectories plotting changes in MMSE performance over time in 62-year old (younger) and 80-year old (older) women in each of the APOE*4 groups. (D) Fitted trajectories plotting changes in memory performance over time in 62-year old (younger) and 80-year old (older) women in each of the APOE*4 groups. NC = Non-carrier; C = Carrier.

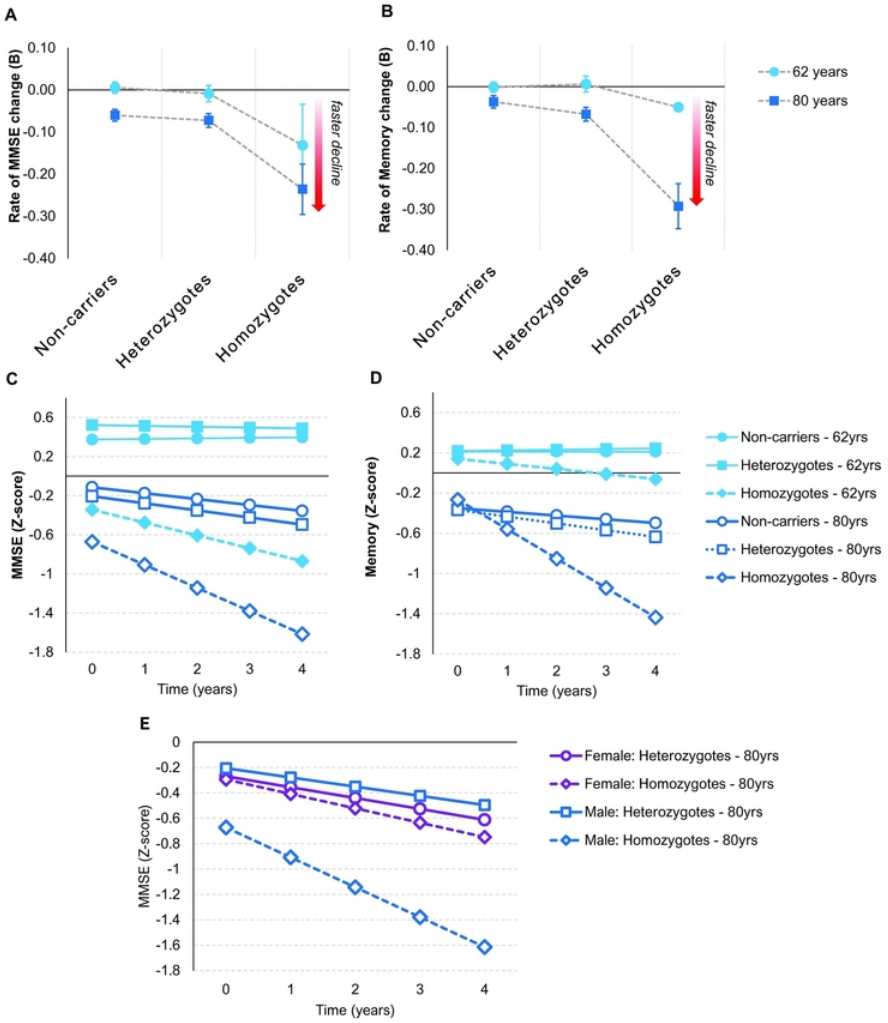

Figure 2. Association between APOE*4 and cognitive decline in men
(A) Mean annual rates of change in MMSE performance and standard errors for men aged 62 years (younger) and 80 years (older) at baseline in each of the APOE*4 groups. (B) Mean annual rates of change in memory performance and standard errors for men aged 62 years (younger) and 80 years (older) at baseline in each of the APOE*4 groups. (C) Fitted trajectories plotting changes in MMSE performance over time in 62-year old (younger) and 80-year old (older) males in each of the APOE*4 groups. (D) Fitted trajectories plotting changes in memory performance over time in 62-year old (younger) and 80-year old (older) males in each of the APOE* groups. (E) Fitted trajectories plotting changes in MMSE scores in 80-year old (older) male and female heterozygotes and homozygotes.

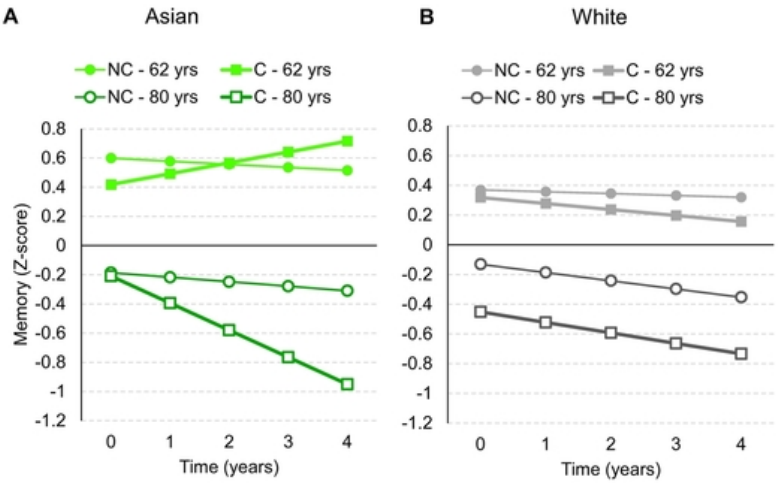

Figure 3. Effects of APOE*4 on cognitive decline in Asian and White men
(A) Fitted trajectories plotting changes in memory performance over time in 62-year old (younger) and 80-year old (older) Asian APOE*4 carriers and non-carriers. (B) Fitted trajectories plotting changes in memory performance over time in 62-year old (younger) and 80-year old (older) White APOE*4 carriers and non-carriers. NC = Non-carrier, C = Carrier.

eTable1. Ethics approvals for the individual contributing studies.

Study	Institutional Review Board
Bambui	Ethics Boards of the Fundac¸a˜o Oswaldo Cruz in Rio de Janeiro and the Instituto Rene´ Rachou of the Fundac¸a˜o Oswaldo Cruz in Belo Horizonte, Brazil (14/2007 - CEPSH-CpqRR)
CFAS	Anglia and Oxford Multi-centre Research Ethics Committee (MREC) - 99/5/22; Eastern MREC – 99/5/22; Eastern MREC – 05/MREO5/37; NRES Committee East of England – 05/MRE05/37
CHAS	Medical University of Havana's Ethics Committee – Approval 20/01/2003
EAS	Albert Einstein College of Medicine Institutional Review Board (Approval#1996-175)
ESPRIT	Ethics committee (CCPPRB) of the Kremlin Bicetre hospital (n° registered 99-28)
HELIAD	Institutional Ethics Review Board of the University of Thessaly (BEY846Ψ8N2-32ΠΙ)
HK-MAPS	Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CRE-2011.101)
Invece.Ab	Ethics Committee of the University of Pavia (#3/2009)
KLOSCAD	Institutional Review Board of Seoul National University Bundang Hospital, Korea (IRB No. B-0912/089-010)
LEILA75+	Ethics committee of the University of Leipzig (C7 79934700)
MoVIES	University of Pittsburgh Institutional Review Board (IRB# 961263-0110)
PATH	Australian National University Human Research Ethics Committee (#M9807, #2002/189, #2006/314, # 2010/542, #2001/2, #2009/039)
SALSA	University of California, San Francisco Human Research Protection Program Institutional Review Board (IRB#10-00243)
SLASI	National University of Singapore Institutional Review Board (Reference Code: 04-140)
Sydney MAS	University of New South Wales Human Research Ethics Committee (approval #14327)

Note.
Written consent was exclusively or predominantly obtained from participants in all studies (SPAH obtained oral consent from illiterate participants; CFAS obtained oral consent, countersigned by a witness, from participants with a physical/visual disability).
Further participant consent was not deemed necessary as only fully de-identified data were shared with the analysis team (e.g., as per the Privacy Rule proposed by the National Institute of Health, USA: http://privacyruleandresearch.nih.gov/research_repositories.asp).

eTable2. Information Relating to Participating COSMIC Studies

Study	Abbreviation	Location	Main race/ethnicity	Sample size[a]	Years run[b]	Reference
Bambui Cohort Study of Aging	Bambui	Bambui, Brazil	Brazilian	1491	1997–2013	Lima-Costa et al. (1)
Cognitive Function & Ageing Study	CFAS	United Kingdom†	White	12256	1989–	Brayne et al.(2)
Cuban Health and Alzheimer Study	CHAS	Havana and Matanzas, Cuba	White, Black, Mixed‡	2574	2003–	Llibre-Rodriguez et al. (3)
Einstein Aging Study	EAS	New York, USA	White, Black§	2063	1993–	Katz et al. (4)
Etude Santé Psychologique et Traitement	ESPRIT	Montpellier, France	White	2187	1999–	Ritchie et al.(5)
Hellenic Longitudinal Investigation of Aging and Diet	HELIAD	Larissa and Marousi, Greece	White	1174	2010–	Dardiotis et al. (6)
Hong Kong Memory and Ageing Prospective Study	HK-MAPS	Hong Kong	Chinese	785	2005–	Wong et al. (7)
Invecchiamento Cerebrale in Abbiategrasso	Invece.Ab	Abbiategrasso, Italy	White	1267	2010–2015	Guaita et al. (8)
Korean Longitudinal Study on Cognitive Aging and Dementia	KLOSCAD	South Korea (nation-wide)	Korean	6513	2009–2018	Kim et al. (9)
Leipzig Longitudinal Study of the Aged	LEILA75+	Leipzig, Germany	White	1040	1997–2014	Riedel-Heller et al. (10)
Monongahela Valley Independent Elders Survey	MoVIES	Mid-Monongahela Valley, PA, USA	White	1613	1987–2002	Ganguli et al.(11)
Personality and Total Health Through Life Project	PATH	Canberra, Australia	White	2545	2001–	Anstey et al.(12)
Sacramento Area Latino Study on Aging	SALSA	Sacramento Valley, CA, USA	Hispanic; Mexican ancestry	1710	1998–2008	Haan et al. (13)
Singapore Longitudinal Ageing Studies (I)	SLASI	Singapore	Chinese	1858	2003–	Feng et al. (14)
Sydney Memory and Ageing Study	Sydney MAS	Sydney, Australia	White	1037	2005–	Sachdev et al.(15)

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eTable3. Information relating to Dementia diagnosis, Tests of Memory and the MMSE, and Data Relating to Risk Factors in all Participating COSMIC Studies

Study	**Criteria used to classify dementia**	**General Cognition test**	**Memory tests**	**Hypertension[a]**	**Cardiovascular disease[b]**	**Diabetes[c]**	**Stroke[d]**
Bambui	MMSE score cut-off point 13/14 appropriate for Brazilian populations with low schooling[f]	MMSE	MMSE 3-word list recall	1. Blood pressure (mean of 2nd and 3rd) 2. Medication	Myocardial infarction or angina	1. Fasting blood glucose 2. Treatment	History of stroke
CFAS	AGECAT organicity level of O3	MMSE	MMSE 3-word list recall	History	Angina or heart attack	History	History of stroke
CHAS	DSM-IV or education-adjusted 10/66 Lancet dementia diagnosis; those with CDR>=1 but not indicated as having a dementia diagnosis were also excluded	Community Screening Instrument for Dementia (CSI-D). Scores converted to MMSE with a published co-calibration table(16)	CERAD 10-word list recall test	1. Blood pressure (average) 2. History indicated by diagnosis or treatment	Doctor diagnosed any of heart attack, angina, heart failure, valve disease, or other (such as atrial fibrillation or ventricular arrhythmia or cardiomyopathy)	1. Told had diabetes 2. Had treatment 3. Fasting blood glucose	Self-report of a clinical diagnosis
EAS	DSM-IV	Blessed Information Memory Concentration test. Validated formula was used to convert these scores to MMSE scores(17).	Free and Cued Selective Reminding Test	1. Blood pressure (mean of 2) 2. History	Myocardial infarction, coronary artery bypass, angina, heart failure, angioplasty, or arrhythmia	History	Medical history of stroke
ESPRIT	Standardized interview by a neurologist incorporating cognitive testing, with diagnoses made using the DSM-IV, validated by an independent panel of expert neurologists	MMSE	MMSE 3-word list recall	1. Blood pressure (mean of 2) 2. Medication	Ischemic heart disease (defined as any of current angina, history of angioplasty, heart operation or myocardial infarction) or heartbeat disorders (arrhythmia or auricular fibrillation)	1. Treatment 2. Fasting blood glucose	Have you had one c more cerebrovascular attacks (strokes, seizures)?
HELIAD	Full battery of neuropsychological tests, neurological examination and a consensus diagnosis of Neurologists and Neuropsychologists using DSM-IV criteria	MMSE	Greek Verbal Learning Test	History	Coronary disease, myocardial infarction, congestive heart failure, arrhythmia, or any other heart disease	History	Medical history of stroke or TIA

Study	Criteria used to classify dementia	General Cognition test	Memory tests	Hypertension[a]	Cardiovascular disease[b]	Diabetes[c]	Stroke[d]
HK-MAPS	Clinical Dementia Rating ≥1	MMSE	ADAS-Cog delayed recall item	Cumulative Illness Rating Scale severity rating 1+	Cumulative Illness Rating Scale severity rating 1+ for either heart disease (ischemic heart disease or heart failure) or arrhythmia/ atrial fibrillation	Cumulative Illness Rating Scale severity rating 1+	Cumulative Illness Rating Scale severi rating 1+ for cerebrovascular disease (CVA, TIA)
Invece.Ab	DSM-IV	MMSE	RAVLT trial 7 (15 min delay)	1. Medication 2. Supine blood pressure 170-180 mmHg and history 3. Supine blood pressure >180 mmHg	1. Cardiovascular disease defined by study as any of myocardial infarction, heart failure, angina, arrhythmia, coronary artery bypass graft, or other 2. Medication 3. Atrial fibrillation	1. Treatment 2. History	History of stroke or TIA
KLOSCAD	DSM-IV	MMSE	CERAD 10-word list recall test	1. History (also having follow-up current status data or age first diagnosed/began medication) 2. Self-reported current 3. Blood pressure (mean of 3)	1. History of any of myocardial infarction, angina, congestive heart failure, arrhythmia, cardiac operation, or other (also having follow-up current status data or age first diagnosed/began medication) 2. Self-reported current cardiac disease	1. History (also having follow-up current status data or age first diagnosed/began medication) 2. Self-reported current 3. Fasting blood glucose 4. Non-fasting blood glucose ≥200mg/dL	History of stroke (sometimes indicate only by having data for a follow-up current status), cerebral infarction, cerebral haemorrhage, TIA, cerebral ischaemia, or "something like stroke".
LEILA75+	DSM-IV	MMSE	MMSE 3-word list recall	1.Blood pressure	Self-reported myocardial infarction	Self-reported	Self-reported histor of stroke
MoVIES	Clinical Dementia Rating ≥1	MMSE	CERAD 10-word list recall test	1. Blood pressure (right or left: n=338; averaged over both: n=67) 2. History	History of any of myocardial infarction, angina, pacemaker, palpitations, heart murmur, or other (includes reported presence >1 month ago at wave 2)	History (includes reported presence >1 month ago at wave 2)	History of stroke (includes participants assesse at wave 2 indicating presence >1 month ago)
PATH	DSM-IV	MMSE	California Verbal Learning Test (recall of first list)	1. Blood pressure (mean of 2) 2. Medication	"Do you have heart trouble?"	1. History 2. Treatment	"Have you ever suffered a stroke?"
SALSA	California ADDTC criteria for vascular dementia and NINDS-ADRDA for Alzheimer's disease	Modified MMSE. Scores converted to MMSE with a published co-calibration table(16)	Spanish and English Verbal Learning Test	1. Blood pressure (mean of 2) 2. Self-reported 3. Medication	Myocardial infarction, angina, congestive heart failure, atrial fibrillation, or heart/coronary catheterization	1. Self-report 2. Fasting blood glucose 3. Medication	Self-report
SLASI	DSM-IV	MMSE	RAVLT trial 7	1. Blood pressure (1 reading) 2. Medication 3. History	1. Heart attack, heart failure, or atrial fibrillation 2. Medication for heart attack, heart failure, or atrial fibrillation	1. Fasting blood glucose 2. Treatment 3. History	History of stroke or regular medication for stroke
Sydney MAS	DSM-IV	MMSE	RAVLT trial 7	1. Blood pressure (mean of 2) 2. Medication 3. History	1. Heart attack, angina, cardiomyopathy, valve disease, arrhythmia, atrial fibrillation	1. Fasting blood glucose 2. Treatment 3. History	Diagnosis of stroke or TIA

[a] Any of systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, taking medication for hypertension, or medical history
[b] History of any relevant condition (heart attack, angina, cardiomyopathy, valve disease, arrhythmia, atrial fibrillation, etc.)
[c] Any of fasting blood glucose ≥126 mg/dL (>7 mmol/L), treatment for diabetes, or medical history
[d] History of stroke or transient ischemic attack
[e] Any of total cholesterol ≥240 mg/dL (>6.2 mmol/L), triglycerides ≥200 mg/dL (>2.3 mmol/L), treatment for high cholesterol, or medical history
[f] Castro-Costa E, Fuzikawa C, Uchoa E, Firmo JO, Lima-Costa MF. Norms for the mini-mental state examination: adjustment of the cut-off point in population-based studies (evidences from the Bambui health aging study). Arq Neuropsiquiatr 2008;66:524-8.

eTable4. Details on APOE*4 measurement in each study

Study	APOE assessment
Bambui	Genomic DNA for ApoE genotyping was extracted from blood samples using the Wizard® Genomic DNA Purification System (Promega, Madison, WI, USA). DNA samples were then amplified by polymerase chain reaction (PCR), followed by digestion with HhaI, and restriction fragment length polymorphism analysis. The DNA samples were subjected to PCR with the following primers: forward 5' TAA GCT TGG CAC GGC TGT CCA AGG A 3' and reverse 5' ACA GAA TTC GCC CCG GCC TGG TAC AC 3'. The PCR conditions were denaturation at 95°C for 5 min, followed by 35 cycles of 95°C for 1 min, 60°C for 1 min, and 70°C for 2 min, and a final extension at 72°C for 10 min. Restriction fragment length polymorphism analysis yielded the

	following patterns: ε2ε2, 91 and 83 bp; ε3ε3, 91, 48 and 35 bp; ε4ε4, 72, 48 and 35 bp. Each of the heterozygote genotypes contained both sets of fragments from each ApoE allele.
CFAS	Cell DNA was extracted from blood samples or buccal swabs for ApoE ε4 genotyping. Apolipoprotein E (APOE) genotyping was identified using polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product (using PCR-restriction fragment length polymorphismanalysis or PCR-RFLP).
CHAS	Cell DNA was extracted from blood samples for ApoE ε4 genotyping. APOE genotyping was identified using polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product (using PCR-RFLP analysis).
EAS	DNA was either extracted from whole blood or isolated from buffy coat stored at −70° using the PuregeneDNA Purification System (Gentra System, Minneapolis). Amplification and sequencing primers for genotyping of target APOE loci (dbSNP ID: rs7412 and rs429358) were designed using PSQ version 1.0.6 software (Biotage); in each case, the reverse primer was biotinylated. Genotyping was performed using a Pyrosequencing PSQ HS 96A system (http://www.pyrosequencing.com) according to manufacturer's instructions.
ESPRIT	Cell DNA was extracted from blood samples for ApoE ε4 genotyping. The specific APOE genotype was identified using polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product (using PCR-RFLP analysis).
HELIAD	ApoE genotyping, available for 1,247 participants was performed in genomic DNA extracted from blood buffy coat, using Qiamp DNA Blood Midi Kits (Qiagen, Venlo, Netherlands).
HK-MAPS	Cell DNA was extracted from blood samples for ApoE ε4 genotyping. The specific APOE genotype was identified using polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product (using PCR-RFLP analysis).
Invece.Ab	Genomic DNA was extracted from blood samples using the Maxwell® 16 system (Promega Corporation, Madison, WI, USA). APOE common variants (ε2, ε3, ε4) were determined from the combination of two SNPs, rs7412 and rs429358. Genotyping analysis was conducted by real-time Polymerase Chain Reaction (PCR) allelic discrimination using TaqMan® probes pre-made assays (Applied Biosystems, Foster City, CA, USA).). Allele calling for all SNPs analyzed by Real Time PCR were based on the clustering algorithm implemented in CFX Manager™ software, version 3.1 (Bio-Rad, USA).
KLOSCAD	Cell DNA was extracted from blood samples for ApoE ε4 genotyping. APOE genotype was then determinedusing polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product (using PCR-RFLP analysis).
LEILA	ApoE genotyping was done using buccal cell DNA and a PCR-Based Assay simultaneously utilizing two distinct restriction enzymes (*Afl*III and *Hae*II) as described in a paper by Zivelin and colleagues (Zivelin A, Rosenberg N, Peretz H, et al. Improved method for genotyping apolipoprotein E polymorphisms by a PCR-based assay simultaneously utilizing two distinct restriction enzymes. Clinical Chemistry. 1997 Sep;43(9):1657-1659).
MoVIES	Cell DNA was extracted from blood samples and then APOE genotype was identified from the extracted cell DNA using polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product (using PCR-RFLP analysis).
PATH	Genomic DNA was extracted from buccal swabs using QIAGEN DNA Blood kits (#51162; QIAGEN, Hilden, Germany). To determine the *APOE* genotype (*APOE *E2, APOE *E3, APOE *E4* alleles), we genotyped two single-nucleotide polymorphisms (SNPs; NCBI SNPs *rs429358* and *rs7412*) using TaqMan assays (Applied Biosystems [ABI], Foster City, CA). DNA (1_l) was added to each well of a 384-well clear optical reaction plates (ABI #4309849) using a liquid handling robot and was dried down at 60° C for 30 min. These plates were then stored at _20° C until required. Two separate TaqMan assays were performed: one for SNP *rs429358* and the other for SNP *rs7412*. Each *APOE* TaqMan assay contained 2.0 _l of TaqMan 2_ universal polymerase chain reaction (PCR) master mix (ABI #4304437), 0.0625 _l of the appropriate 80_ assay mix containing the SNP-specific primers and probes (TaqMan genotyping assays), and H2O to a total volume of 5 _l. A liquid-handling robot dispensed this mix into each well containing the dried-down DNA. Plates were then sealed with optical adhesive covers (ABI #4311971), spun briefly (4,000 rpm for 2 min), and placed into an 7900HT real-time PCR machine (ABI). The cycling program was as follows: 95° C for 10 min, followed by 40 cycles of 95° C for 15 s and 60° C for 1 min. Allelic discrimination was automated using the manufacturer's software (Applied Biosystems, 2004). Positive controls, consisting of DNA of each of the six possible *APOE* genotypes (**E2/*E2, *E2/*E3, *E2/*E4, *E3/*E3, *E3/ *E4, *E4/*E4*), were included on each genotyping plate. These six controls were genotyped using an alternative genotyping method. In this method, a fragment of the *APOE* gene was amplified using PCR and then digested with the restriction endonuclease *Cfo1* (Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res. 1990 Mar;31(3):545-8.). The resulting digested products were resolved on an agarose gel, and the *APOE* genotypes were deduced from the observed combinations of different-sized fragments. Genotype scorers were blinded to the identity of the samples.
SALSA	ApoE genotyping was done using buccal cell DNA. The method used followed a modification of polymerase chain reaction amplification/Hhal restriction isotyping method.
SLASI	Cell DNA was extracted from blood samples for ApoE ε4 genotyping. The specific APOE genotype was identified using polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product (using PCR-RFLP analysis).
Sydney MAS	DNA was extracted from peripheral blood leukocytes or saliva samples at Genetics Repositories Australia (www.powmri.edu.au/GRA.htm) using standard procedures. As an initial analysis, apolipoprotein E (APOE) genotyping was undertaken. The two single nucleotide polymorphisms (rs7412 and rs429358), which distinguish between the three APOE alleles ε2, ε3 and ε4 were genotyped using Taqman assays (Applied Biosystems Inc. (ABI), Foster City, CA, U.S.A.). The validity of the genotyping was confirmed in a subsample by employing an alternate genotyping method that uses polymerase chain reaction amplification and restriction digest analysis

eTable5: *Number Of Assessment Waves, Time Since Baseline (Yrs, Mean±SD), and Number of Individuals With MMSE Scores at each Wave*[a]

	Waves	Years in study	Years in study	Wave 1	Wave 2			Wave 3			Wave 4			Wave 5			Wave 6			Wave 7		
	Total	M	(max)	N	N	M	SD	N	M	SD	N	M	SD	N	M	SD	N	M	SD	N	M	SD
BAMBUI	16	9.7	15	1313	1225	1	0	1151	2	0	1094	3	0	1028	4	0	985	5	0	912	6	0

CAS	2	3.3	7.6	1946	1390	4.7	0.9															
CFAS	3	5.5	11.9	969	950	2.1	0.1	442	9.9	0.7												
EAS	16	4.4	19.6	873	696	1.2	0.4	571	2.4	0.6	479	3.5	0.8	407	4.6	0.9	337	5.6	0.9	265	6.6	1.1
ESPRIT	4	5.4	9	2108	1849	1.7	0.2	1602	3.8	0.2	1212	7.6	0.2									
HELIAD	2	1.2	6.76	1112	590	2.6	0.7	153	5.5	0.3												
HK-MAPS	3	3.7	6.18	1168	1019	2.2	0.2															
Invece.Ab	2	1.8	3.28	3512	2860	2.1	0.3															
KLOSCAD	2	1.7	4	243	241	1.7	0.2	235	3	0.1	243	4.5	0.1	172	6.2	0.2	154	7.2	0.3	28	14.9	0.5
LEILA	7	7.3	15.7	215	215	2	0.2	208	4.3	0.4	211	6.6	0.5	179	9	0.5	127	11.4	0.7	62	13.5	0.5
MoVIES	7	10.7	14.5	215	208	4.26	0.45	211	6.58	0.49	179	8.97	0.54	127	11.40	0.66	62	13.48	0.50	208	4.26	0.45
PATH	3	6.7	9.07	2367	2059	4.1	0.2	1816	8.1	0.3												
SALSA	7	5.7	9.39	1538	1112	2.21	0.23	1080	3.42	0.41	944	5.42	0.62	827	6.78	0.53	741	8.07	0.47	1112	2.21	0.23
SLASI	3	2.0	4.53	788	535	1.6	0.5	300	3.9	0.2												
SydneyMAS	4	4.7	6.78	953	844	1.9	0.1	741	4	0.2	645	5.9	0.2									
Total				19225																		
				Cont'd	**Wave 8**			**Wave 9**			**Wave 10**			**Wave 11**			**Wave 12**			**Wave 13**		
					N	**M**	**SD**	**N**	**M**	**SD**	**N**	**M**	**SD**	**N**	**M**	**SD**	**N**	**M**	**SD**	**N**	**M**	**SD**
				BAMBUI	931	7.00	0.00	793	8.00	0.00	732	9.00	0.00	644	10.00	0.00	641	11.00	0.00	563	12.00	0.00
				EAS	200	7.59	0.96	124	8.61	1.07	84	9.70	1.19	63	10.85	1.46	54	11.67	0.89	43	12.70	0.85
				Cont'd	**Wave 14**			**Wave 15**			**Wave 16**											
					N	**M**	**SD**	**N**	**M**	**SD**	**N**	**M**	**SD**									
				BAMBUI	547	13.00	0.00	409	14.00	0.00	349	15.00	0.00									
				EAS	25	13.63	1.02	7	14.49	0.38	2	15.08	0.03									

eTable6: *Proportion of Participants in Each Study Reporting Vascular Risk Factors at Baseline*

		Covariates [a]					
		HT	DIAB	CVD	Stroke	CHOL [b]	Smoking [b]
	N	%	%	%	%	%	%
Bambui	1313	68.3	14.5	15.7	3.3	50.2	17.5 [c]
CFAS	1957	32.4	5.5	18.1	5.6	29.6	19.4
CHAS	977	75.4	30.5	30.6	6.1	6.5	19.9
EAS	873	65.1	16.5	33.7	9.2	57.3	6.9
ESPRIT	2118	71.7	9.1	20.1	3.3	41.5	6.6
HELIAD	901	68.8	18.3	25.4	8.4	14	9.6
HK-MAPS	255	46.7	12.2	14.5	5.5	33.6	14.8
Invece.Ab	1210	60.7	17.3	26.9	7.8	44.8	9.6
KLOSCAD	3517	60.9	25	13.7	9	[d]	11.7
LEILA	243	79.4	22.6	7.8	5.3	[d]	5.8
MoVIES	215	66	8.8	32.6	6	[d]	7
PATH	2367	65.8	7.6	15	4.5	22.9	10.2
SALSA	1538	68.7	32.8	22.4	8.6	50.3	11.2
SLASI	788	61.4	14.6	9.9	2.5	47.2	6.5
Sydney MAS	953	83.3	15.2	29.5	4	68.9	3

Abbreviations: CHOL = high cholesterol, CVD = Cardiovascular disease, DIAB = diabetes, HT = hypertension, [a] Values in percentages are in relation to the included sample of the study displayed in the column labelled *N*. [b] Current smoking and high cholesterol were not used as covariates in the analysis as data for these variables was not available in all studies [c] Bambui did not have data on individuals who were non-smokers. The value reflects the proportion of participants reporting being a current smoker. [d] High cholesterol data was not available in these studies

eTable7. *Results of Metaregression Examining the Moderating Effect of Vascular Risk Factors on APOE*4*

Effect of *APOE*4* on memory decline: absence of risk factors [a]					
Old [c]	-0.013	(-0.053, 0.026)	-0.058	(-0.106, -0.011)*	0.513
Young [c]	0.008	(-0.019, 0.034)	0.016	(-0.041, 0.072)	0.58
Change in effect of *APOE*4* on memory decline with one additional risk factor [b]					
Old [c]	-0.004	(-0.037, 0.029)	0.017	(-0.009, 0.044)	0.791
Young [c]	-0.017	(-0.029, -0.005)**	-0.012	(-0.042, 0.019)	0.691
Effect of *APOE*4* on MMSE decline: absence of risk factors [a]					
Old [c]	-0.033	(-0.082, 0.017)	-0.082	(-0.12, -0.044)***	0.197
Young [c]	-0.007	(-0.035, 0.021)	-0.004	(-0.03, 0.022)	0.611
Change in effect of *APOE*4* on MMSE decline with one additional risk factor [b]					
Old [c]	0.005	(-0.028, 0.038)	0.04	(0.006, 0.074)*	0.775
Young [c]	-0.003	(-0.02, 0.013)	-0.005	(-0.019, 0.008)	0.691

[g] Values reflect the *B*-coefficients for the *APOE*4* group x time interaction term. Negative *B*-values indicate a faster rate of cognitive decline on the specified outcome measure in *APOE*4* carriers relative to non-carriers, in the absence of vascular risk factors. [h] Values reflect the *B*-coefficients for the *APOE*4* group x time x VRISK interaction term. Negative *B*-values indicate that if *APOE*4* (or carriage of two versus one *APOE*4* alleles) is related to faster decline in the absence of risk factors, this effect increases with every additional vascular risk factor. [c] Effects in 'young' and 'old' participants were obtained by estimating model terms at 62-years and 80-years respectively.

eTable8. *Results of Metaregression Comparing Association Between APOE*4 and Cognitive Decline in Whites Versus Asians.*

		Carrier v non-carrier						**Homozygotes versus heterozygotes (dose response effect)**					
		Asian		**White**		**Difference**		**Asian**		**White**		**Difference**	
Outcome	**Age group**	**B**	**CI**	**B**	**CI**	**B**	**CI**	**B**	**CI**	**B**	**CI**	**B**	**CI**
Memory	**Effect of *APOE*4* on cognitive decline** [a]												
	Overall [b]	-0.022	(-0.062, 0.017)	-0.017	(-0.033, -0.001)*	0.006	(-0.037, 0.048)	-0.086	(-0.285, 0.114)	-0.049	(-0.149, 0.05)	0.036	(-0.187, 0.259)
	Old [c]	-0.136	(-0.23, -0.041)*	-0.009	(-0.052, 0.034)	0.127	(0.022, 0.231)*	0.056	(-0.357, 0.469)	-0.224	(-0.441, -0.008)*	-0.28	(-0.746, 0.185)
	Young [c]	0.032	(-0.03, 0.094)	-0.022	(-0.04, -0.004)*	-0.054	(-0.119, 0.011)	-0.229	(-0.593, 0.135)	0.036	(-0.164, 0.235)	0.265	(-0.151, 0.68)

MMSE	**Effect of *APOE*4* on cognitive decline**												
	Overall	-0.008	(-0.048, 0.033)	-0.027	(-0.044, -0.011)**	-0.020	(-0.063, 0.024)	0.279	(-0.342, 0.901)	-0.147	(-0.516, 0.222)	-0.426	(-1.148, 0.297)
	Old	0.009	(-0.079, 0.097)	-0.031	(-0.06, -0.002)*	-0.040	(-0.133, 0.052)	0.170	(-0.531, 0.871)	-0.046	(-0.456, 0.364)	-0.216	(-1.028, 0.596)
	Young	0.020	(0.008, 0.031)	-0.005	(-0.038, 0.027)	0.025	(-0.009, 0.060)	0.343	(-0.572, 1.258)	-0.258	(-0.823, 0.306)	-0.601	(-1.677, 0.474)
Effect of vascular risk factors on association between *APOE*4* and performance													
Memory	**Effect of *APOE*4* on cognitive decline in absence of risk factors** [e]												
	Overall	0.025	(-0.151, 0.201)	-0.015	(-0.091, 0.061)	-0.040	(-0.232, 0.152)						
	Change in effect of *APOE*4* on cognitive decline with additional risk factor [f]												
	Overall	-0.032	(-0.2, 0.137)	0.000	(-0.082, 0.082)	0.032	(-0.156, 0.219)						
MMSE	**Effect of *APOE*4* on cognitive decline in absence of risk factors**												
	Overall	-0.108	(-0.194, -0.022)*	-0.040	(-0.079, -0.001)*	0.068	(-0.027, 0.162)						
	Change in effect of *APOE*4* on cognitive decline with additional risk factor												
	Overall	0.085	(0.024, 0.145)*	0.013	(-0.019, 0.044)	-0.072	(-0.14, -0.004)*						

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. [a] Values reflect *B*-coefficients for the *APOE*4* group x time interaction term. Negative *B*-values indicate a faster rate of cognitive decline on the specified outcome measure in *APOE*4* carriers, or in homozygotes compares to heterozygotes. [b] Overall effects refer to analyses where age was centred at the mean age at baseline of 72 years. [c] Effects in 'young' and 'old' participants were obtained in separate pooled analyses where baseline age was recentred in study-wise GEE models at 62-years and 80-years respectively. [d] Values reflect *B*-coefficients for the *APOE*4* group x time x baseline age interaction term. Negative *B*-values for the effect of age indicates that if *APOE*4* (or carriage of two versus one *APOE*4* alleles) is related to faster decline, this effect increases with every 1-year increase in age at baseline. [e] Values reflect the *B*-coefficients for the *APOE*4* group x time interaction term. Negative *B*-values indicate a faster rate of cognitive decline on the specified outcome measure in *APOE*4 carriers relative to non-carriers, in the absence of vascular risk factors. Blank cells for the comparison between homozygotes and heterozygotes because this analysis was not undertaken due to small numbers.* [f] *Values reflect the B-coefficients for the APOE*4 group x time x VRISK interaction term. Negative B-values indicate that if APOE*4 (or carriage of two versus one APOE*4 alleles) is related to faster decline in the absence of risk factors, this effect increases with every additional vascular risk factor.*

eTable9. *Proportion of Younger and Older Men and Women With High And Low VRISK Scores, Having Each of the Individual Vascular Risk Factors Contributing to VRISK scores*

			Risk Factor					
Sex	**Age**	**VRISK Group**	**Current smoking (%)**	**Heart disease (%)**	**Diabetes (%)**	**High Cholesterol (%)**	**Hypertension (%)**	**Stroke (%)**
Female	**Older** [a]	**High VRISK** [c]	17.4	82.6	79.8	89.9	99.4	42.1
		Low VRISK [d]	4.5	20.8	15.8	34.4	71.1	4.6
	Younger [b]	**High VRISK**	30.5	80.5	78.6	87.4	98.5	36.3
		Low VRISK	7.2	13.4	14.3	39.8	60	3.5
Male	**Older**	**High VRISK**	31.9	81.9	75	85.6	97.3	46.3
		Low VRISK	12.5	26.3	15.9	28.3	67.5	6.5
	Younger	**High VRISK**	40.6	71.9	77.8	88.9	97.1	38.3
		Low VRISK	17.1	15.7	14.6	32.3	62.3	4.3

[a] Older participants are those aged above the median age of 72 years at baseline [b] Younger participants are those aged below the median age of 72 years at baseline [c] High VRISK refers to participants with a VRISK score greater than 3 (out of 6) [d]Low VRISK refers to participants with a VRISK score less than or equal to 3 (out of 6)

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