*Title page

Education and the moderating roles of age, sex, ethnicity and apolipoprotein epsilon 4 on the risk of cognitive impairment

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05-May-2020

Dear Dr. Liang-Kung Chen, Chief Editor,

Thank you for allowing us the opportunity to submit a revised version of our manuscript, AGG-D-19-00403: *Education and the moderating roles of age, sex, ethnicity and apolipoprotein epsilon 4 on the risk of cognitive impairment* to the Archives of Gerontology and Geriatrics. We appreciate the comments you and the reviewers have provided us with in order to improve the manuscript, and hopefully, lead to its publication. I want to sincerely thank the staff at AGG for kindly extending the resubmission date. Below we go through, point-by-point, how we addressed each of the reviewers' comments.

We sincerely hope you are faring well at this time,

Best wishes,

Steve Makkar

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Editor comments

- We have now provided a highlights section in line with the requirements
- Figures are now provided as separate .eps files
- We have converted the abstract into a structured abstract at the request of Reviewer 2

Reviewers' comments:

Reviewer #1:

Specific comments:

In METHODS Study Selection:
The details of participating studies are provided in eTable 2 not in eTable 1
The details of ethics approval are provided in eTable 1 not in eTable 2
In METHODS Study Selection:
The information on the MMSE scores is provided in eTable 3 not eTable 2

- *Thank you for pointing out these errors; We have made the changes within the text, ensuring they point to the correct tables (on page 5, and*

In RESULTS:
Incorrect links to figures 3 A, B, C and D in the text.

- *The correct references to the figures have been added on the bottom of page 10*

In TABLE 2:
In the legend to table the following information is unnecessary as it concerns Table 3:
a Reference Group
b Because of the small numbers of Black APOE*4 carriers in the low education groups, the Elementary and Incomplete Elementary groups were collapsed and treated as the reference education group.

- *This has now been removed.*

In SUPLEMENTARY TABLES:
The number of participating studies were different in eTables 1-4.

- *Thank you this has now been fixed in the list of Supplementary Tables*

Reviewer #2:

Abstract
Include subtitles Background; Objectives; Methods… see AGG journal guidelines.
Include stats to support results.
Give the main clinical and/or social implication of the results at the end of abstract.

- *We have now made the abstract structured. The final sentence of abstract emphasises the possibility that the ethnoregional differences that we found may be due to variations in social, economic, and political outcomes relating to educational attainment, in combination with neurobiological and genetic differences, and warrant further study.*
- *We have also added the hazard ratios and p-values for hypothesis tests of the highlighted results.*

Background
Cognitive reserve or cognitive plasticity or brain reserve capacity is the key term of this manuscript. Please explore it in the Introduction including the cerebral plasticity and ageing implications

- *We have provided a more expanded description of Cognitive reserve in the introduction on Page 3, describing it in relation to enhanced plasticity, namely more efficient brain networks and neural capacity, in combination with better compensatory processes and utilisation of alternative neural pathways.*

Conclusions
The sentences "We speculate that poor-quality Elementary Education available to Asians and Blacks in previous decades may not have built a sufficient level of cognitive reserve to overcome APOE*4-mediated cognitive impairments in these ethnic groups." And "The emergent ethnic differences may be attributable to historically wider gaps in socioeconomic status, employment opportunities, income, and health between low and high educated individuals in Asian and Black, versus White populations" are well-written, however they are missing a clinical and social interpretation of the results, bringing the challenges of ageing in the different countries and considering income, cultural and the political context.

- *Our conclusion has now been expanded on Page 17, where we highlight that the observed ethnoregional differences could potentially be explained by a multitude of social, political, neurobiological, genetic, and economic factor, but because of the data limitations, this cannot be verified in the present study. Data limitations are partly due to the fact that normative studies of ageing have mainly been limited to non-Latino white individuals. We further discuss that if such rich data is available, then the study of ethnoregional differences in ageing should ideally, in the future, look towards utilising complex systems models, where the interrelationships between risk factors and the multitude of social, political, economic factors can be examined as a whole.*

Highlights

- We examined the association between education and cognitive impairment (CI)
- Moderating influences of age, sex, ethnicity, and APOE*4 carriage were tested
- Higher education was related to lower CI risk, but this effect weakened with age
- The effect of education on lower CI risk was stronger in women than men
- High School education lowered CI risk in Blacks and Asians, but not Whites

Abstract

Background:

We examined how the relationship between education and latelife cognitive impairment (defined as a Mini Mental State Examination score below 24) is influenced by age, sex, ethnicity, and Apolipoprotein E epsilon 4 (*APOE*4*).

Methods

Participants were 30,785 dementia-free individuals aged 55-103 years, from 18 longitudinal cohort studies, with an average follow-up ranging between 2 and 10 years. Pooled hazard ratios were obtained from multilevel parametric survival analyses predicting cognitive impairment (CI) from education and its interactions with baseline age, sex, *APOE*4* and ethnicity. In separate models, education was treated as continuous (years) and categorical, with participants assigned to one of four education completion levels: Incomplete Elementary; Elementary; Middle; and High School.

Results

Compared to Elementary, Middle (HR=0.645, P=0.004) and High School (HR=0.472, P < 0.001) education were related to reduced CI risk. The decreased risk of CI associated with Middle education weakened with older baseline age (HR=1.029, P=0.056) and was stronger in women than men (HR=1.309, P=0.001). The association between High School and lowered CI risk, however, was not moderated by sex or baseline age, but was stronger in Asians than Whites (*HR*=1.047, P=0.044), and significant among Asian (HR=0.34, P < 0.001) and Black (HR=0.382, P=0.016), but not White, *APOE*4* carriers.

Conclusion

High School completion may reduce risk of CI associated with advancing age and *APOE*4*. The observed ethnoregional differences in this effect are potentially due to variations in social, economic, and political outcomes associated with educational attainment, in combination with neurobiological and genetic differences, and warrant further study.

The attainment of higher levels of education is related to decreased dementia incidence (Caamano-Isorna et al., 2006; Meng and D'Arcy, 2012; Sharp and Gatz, 2011; Valenzuela and Sachdev, 2006; Xu et al., 2016), and attenuated cognitive decline (Albert et al., 1995; Alley et al., 2007; Anstey and Christensen, 2000a; Anstey and Christensen, 2000b; Anstey et al., 2003; Bosma et al., 2003; Christensen et al., 1997; Colsher and Wallace, 1991; Hall et al., 2007; Leibovici et al., 1996; Zahodne et al., 2015). It has been theorised that this is in part due to education building *cognitive reserve* (CR) or brain reserve capacity. Cognitive reserve may be characterised as more efficient brain networks and greater neural capacity, making the brain less prone to disruption. It may also reflect better compensatory neural processes in the face of neural damage, including the use of alternative brain structures and neural pathways which are normally unused by those with intact brains (Meng and D'Arcy, 2012; Stern et al., 1999). The cognitive reserve hypothesis is supported by studies finding higher levels of brain pathology and degraded functioning among AD sufferers with high versus low educational attainment, despite having comparable levels of cognitive impairment (Fratiglioni and Wang, 2007). Because of this cognitive reserve, individuals are better able to tolerate age-related neuropathology without the expression of marked cognitive impairment(Meng and D'Arcy, 2012; Stern et al., 1999). As the degree of neuropathology advances over time, however, it may be so severe that the brain can no longer compensate for the underlying physical damage, thus leading to accelerated cognitive decline (Stern et al., 1999). This would imply that higher education may not be related to attenuated decline at very old ages (Van Dijk et al., 2008). This hypothesis has been supported by some(Butler et al., 1996; Schmand et al., 1997), but not all studies (Farmer et al., 1995; Van Dijk et al., 2008), highlighting the need for clarification.

Recent studies also indicate that the relationship between education and attenuated cognitive decline is *curvilinear*, meaning that after a certain level of educational attainment, additional

education does not contribute to further significant reductions in cognitive decline(Wilson et al., 2009). Two U.S. based studies have suggested that this may occur after completion of 8-9 years (Lyketsos et al., 1999; Zahodne et al., 2015) of formal education (i.e., *middle school*). Whether this inference can be generalised to different cohorts and settings remains to be determined.

Compared to men, women with lower education are more likely to develop dementia (Launer et al., 1999; Ott et al., 1999; Russ et al., 2013; Sharp and Gatz, 2011); however, it is currently unclear if they also decline faster. Ethnoregional differences in the relationship between education and cognitive decline are also unclear, particularly differences to Asian groups, as prior studies have mainly compared White and Black Americans (Fitzpatrick et al., 2004; Lopez et al., 2017; Sachs-Ericsson and Blazer, 2005). Finally, there are mixed results surrounding whether education can offset faster cognitive decline associated with carriage of the Apolipoprotein E epsilon 4 (*APOE*4*) allele (Duara et al., 1996; Seeman et al., 2005; Shadlen et al., 2005; Vermeiren et al., 2013; Winnock et al., 2002). Studies incorporating larger, and more diverse study samples may help to clarify these important issues.

Therefore, we aimed to pool harmonised data from 18 independent research studies participating in COSMIC (Cohort Studies of Memory in an International Consortium) to clarify the nature of the relationship between education and cognitive decline in an ethnically diverse group of older adults, and to determine how this relationship is moderated by age, sex, ethnicity, and *APOE*4* carriage.

Methods

Study Selection

We collected datasets for this meta-analysis from independent research studies participating in COSMIC; a consortium which combines data from longitudinal, population-based cohort

studies of older adults to identify factors that moderate the risk of cognitive decline(Sachdev et al., 2013). Studies were included if they collected the following Individual Participant Data (IPD) at baseline: age, sex, education (in years), data for four dementia risk factors to be treated as covariates (i.e., hypertension, diabetes, history of cardiovascular disease, history of stroke), score for a test of general mental status or cognition (typically the Mini Mental State Examination [MMSE]), self-reported ethnicity, and dementia status (details of participating studies are provided in eTable 1). For studies lacking IPD for ethnicity, participants' ethnicity was assigned as the majority ethnicity of the study sample (as informed by each study's lead investigators). Criteria used to diagnose dementia as well as risk factor data available in each study, and how this was harmonised across studies is provided in eTable 2. Participants that did not have the requisite data specified above, or who had dementia at baseline were excluded from all analyses. 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 meta-analysis had prior ethics approval (see eTable 3 in the Supplement).

Outcome Measure

The MMSE(Folstein et al., 1975) was the primary outcome measure in this study, which was administered in all but three studies. In these three studies an alternative test of general mental status was administered, and scores converted to MMSE scores using published algorithms or co-calibration tables (see eTable 2). MMSE scores were then converted to a binary indicator, where scores ≤ 23 indicated the presence of cognitive impairment (Tombaugh and McIntyre, 1992a; Tombaugh and McIntyre, 1992b). This cut-off has shown good sensitivity and specificity for the classification of dementia (Kochhann et al., 2010).

Synthesis Methods

A one-step IPD meta-analysis was conducted using multilevel parametric survival analysis to examine the relationship between education and risk of cognitive impairment (CI). The multilevel model included two levels (i.e., participants nested in studies). Multivariate survival analysis with ordered failure events was used to account for participants who were cognitively impaired at multiple study waves (Andersen and Gill, 1982; Twisk, 2013). For all participants, *event time* was the time (in years) at which cognitive impairment, or when censoring occurred. A *start time* variable coded the time when participants began being at risk of cognitive impairment. For censored observations, start time was 0 (i.e., time of entry into the study). For participants who experienced CI, on their subsequent dataset row, start time was the time point when they were last cognitively impaired (i.e., their most recent "failure").

Models were fit using the mestreg package in Stata 15 (StataCorp., 2013). Model terms included education in years (centred at the mean of 8.9 years), education^2, baseline age (centred at the median age of 70 years), and the interaction between both education and education^2 with baseline age (i.e., *education* x *age; education*^{2} x *age*). Covariates were sex, hypertension, diabetes, history of cardiovascular disease, history of stroke and MMSE score at baseline. To examine whether associations with education differed between sexes, two additional interactions were included: *education x sex,* and *education*^{2} *x sex*. Robust standard errors were calculated which adjusted for multiple CI events in individuals. Based on tests of model fit using likelihood ratio tests, random effects for the intercept and slope (i.e., for education), and their covariance, were included in the analysis, and a Weibull distribution was selected.

The above analyses were repeated treating education as categorical. We categorised participants into the following levels of educational attainment: (i) Incomplete Elementary; (ii) Elementary; (iii) Middle Level/Incomplete High School; and (iv) High School. The

Elementary category was treated as the reference group. If a study collected categorical educational data, participants were assigned to one of the above-mentioned categories using this data. In studies, with minimal or no available categorical data, we used the continuous years of education data to assign participants to an educational achievement level based on cut-offs specific to the country where the study was conducted (see eTable 4), which were obtained from the Scholaro website (https://www.scholaro.com).

To explore ethnic differences, we included a categorical variable in the analysis that coded ethnicity (0 = White, 1 = East/Southeast Asian, 2 = Black), and all interactions (i.e., 2-way, and 3-way) with education category and baseline age. Whites were treated as the reference. To examine whether *APOE*4* carriage moderated the association between education and cognitive impairment, we repeated the analyses above, and included a binary indicator for *APOE*4* (1 = carrier, 0 = non-carrier) and all interactions with education category and baseline age. To test for ethnic differences in the interaction between *APOE*4* and education, we included all interactions between ethnicity, *APOE*4*, and education category.

To minimise bias associated with non-random attrition, we incorporated inverse probability weighting (IPW) into all analyses(Buchanan et al., 2014). To calculate IPWs, logistic regression was used to regress a binary indicator of missingness (1 = not missing; 0 = missing) for each outcome at each wave on participants' sex, age at last measurement, years of education (and all interactions between age, sex, and education), presence of hypertension, diabetes, heart disease, and stroke, and their MMSE score, age, and time in study from their most recently completed data collection point. Predicted probabilities from each model were converted to stabilised IPWs and used as a scale weight in the analysis (Singer and Willet, 2003; Tabachnick, 2007; Thoemmes and Ong, 2015).

Results

Participant characteristics

Baseline demographic characteristics are shown Table 1. The average follow-up duration ranged between 2 and 10 years, and the mean age at baseline ranged between 63 and 81 years. The proportion of participants lost to follow-up ranged between 1% (Tajiri) and 99.9% (EAS). The rate of attrition was positively associated with the length of follow up (R = 0.9, P < 0.001). In all but two studies (PATH, MoVIES), females outnumbered males. Mean years of education ranged between 2.8 and 13.9 years across studies, with an overall mean of 9 years. For 10 studies, the majority educational attainment level was at least Middle school, whereas for the remaining 8 studies, most participants had either a complete or incomplete Elementary education. The proportion of participants who were *APOE*4* carriers ranged between 13.3 and 25.2%. IPD for ethnicity was available in six studies (Bambui, EAS, MoVIES, PATH, SydneyMAS, CHAS). In ten studies, the majority of the sample (i.e., > 60%) was White. Six studies included Asian participants. In three of these studies, the entire sample comprised of Asians. Five studies had Black participants, with the proportion ranging between 0.2 to 27.1% of the study sample. The proportion of participants that experienced cognitive impairment ranged from 2% (PATH) to 62% (Bambui).

Association between education and cognitive impairment

Results are displayed in Table 2. Overall, more years of education was related to decreased CI risk (HR=0.881, P < 0.001). The quadratic term for education ($education^2$), was small, but significant (HR=1.003, P=0.031), implying that the association between education and decreased CI risk was less pronounced at higher levels of education. Both the linear (HR=1.006, P < 0.001) and quadratic terms (HR=0.999, P=0.002) for education significantly weakened with older baseline age but were not moderated by sex.

We further explored this nonlinearity by examining education categorically. With Elementary education as the reference, the risk of CI was significantly higher for incomplete Elementary (HR=1.645, $P < 0.001$), and lower for both Middle (HR=0.645, $P=0.004$) and High School education (HR=0.472, $P < 0.001$; See Figure 1A). Additional comparisons showed that CI risk was lower for High School versus Middle education (HR=0.73, $P=0.002$). Furthermore, we separated the High School category into those that did and did not complete College Education and found no difference in CI risk between these groups (HR=0.762, $P=0.234$).

Differences in CI risk between both Incomplete Elementary (HR=0.955, $P < 0.001$; Figure 1B) and Middle education (HR =1.038, $P < 0.001$; Figure 1C) compared to Elementary education significantly weakened with older baseline age, but not so for High School education (HR=1.029, $P=0.056$). Simple effect comparisons showed that among 60 but not 80-year olds, the risk of CI was higher for incomplete Elementary (HR=2.601, $P < 0.001$), and lower for Middle versus Elementary education (HR=0.444, $P=0.003$). High School education, however, was related to decreased CI risk in both 60 (HR=0.353, $P < 0.003$) and 80-year olds (HR=0.631, $P < 0.001$).

Examining sex differences, the reduction in CI risk associated with Middle versus Elementary education was significant for women (HR=0.58, $P < 0.001$) but not men (HR=0.76, $P=0.128$), and this sex difference was significant (HR=1.309, $P=0.001$) as shown in Figure 1C. There were no sex differences in CI risk for either the Incomplete Elementary or High School categories (versus Elementary education).

As shown in Table 3, in both Asians and Whites, incomplete Elementary education was related to a significant increase in CI risk, whereas Middle and High School education were both related to a significant decrease in CI risk, relative to Elementary education. The reduction in CI risk associated with High School education, however, was significantly larger

in Asians than Whites (HR=0.575, *P*=0.002), as can be seen in Figure 2A. In addition, the reduction in CI risk associated with High School completion weakened with older baseline age to a stronger degree in Asians than Whites (*HR*=1.047, *P*=0.044).

Although differences between Whites and Blacks were not significant for each of the comparisons, Table 3 shows that neither Middle (versus Elementary), nor Elementary (versus incomplete Elementary) education were related to significant reductions in CI risk among Blacks. High School versus Elementary education, however, was related to significant reduction CI risk among Blacks (HR=0.459, *P*=0.001), as shown in Figure 2B.

As shown in Table 2, *APOE*4* carriage did not moderate differences in CI risk between education levels (treating Elementary education as the reference), and these associations were not moderated by baseline age or sex. Results in Table 2 nonetheless show that Elementary (versus incomplete Elementary) and Middle (versus Elementary) education were related to significant reductions in CI risk in non-carriers only. High School completion, however, was associated with a lowered risk of CI compared to Elementary education in both *APOE*4* carriers (HR=0.52, *P*=0.007) and non-carriers (HR=0.519, *P*=0.009).

As shown in Table 3, *APOE*4* carriage moderated the associations between Incomplete Elementary (HR=0.555, *P*=0.018) and Middle education (HR=0.304, $P < 0.001$) with CI risk differently in Whites and Asians. In Whites, Incomplete versus Complete Elementary education was associated with increased CI risk in both *APOE*4* carriers (HR=2.395, *P*=0.004) and non-carriers (HR=1.834, *P*=0.001). In Asians, however, this difference was significant for non-carriers only (HR=1.572, *P*=0.003). As shown in Figure 3A, however, Middle level (versus Elementary) education was significantly related to decreased CI risk in both Asian *APOE*4* carriers (HR=0.34, $P < 0.001$) and non-carriers (HR=0.493, $P < 0.001$); whereas in Whites, as shown in Figure 3B, this reduction in CI risk only emerged for non-

carriers (HR=0.382, *P*<0.001). Similar results emerged for the comparison between High School and Elementary education, although the difference between Whites and Asians was not significant.

The interaction between *APOE*4* and education on CI risk did not significantly differ between Whites and Blacks, at any educational level. Nonetheless, results in Table 3 indicate that Elementary and Middle education were unrelated to decreased CI risk in both Black *APOE*4* carriers and non-carriers. High School education was related to decreased CI risk in Black *APOE*4* carriers (HR=0.382, *P*=0.016), but not non-carriers, as can be seen in Figure 3C. In Whites (Figure 3D), the opposite was found, with High School education being associated with a significant decrease in CI risk in non-carriers (HR=0.448, *P*=0.002), but not in *APOE*4* carriers.

discussion

In this IPD meta-analysis, years of education was associated with a significant reduction in the risk of cognitive impairment (CI). This association, however, was non-linear, indicating that with even more years of education, the reduction in CI risk was less pronounced. Categorical analyses clarified these findings, indicating that increasing levels of educational attainment (i.e., Elementary versus Incomplete Elementary, Middle versus Elementary, and High School versus Middle) were each significantly related to decreases in CI risk. Additional analyses revealed, however, that completion of College did not decrease CI risk relative to the completion of High School. Expanding upon previous systematic reviews (Caamano-Isorna et al., 2006; Meng and D'Arcy, 2012; Sharp and Gatz, 2011; Valenzuela and Sachdev, 2006; Xu et al., 2016), our results imply that the association between education and reduction in cognitive impairment risk is not monotonically linear, in line with recent studies conducted in individual cohorts (Lyketsos et al., 1999; Wilson et al., 2009; Zahodne et al., 2015).

Our results align with those of Zahodne et al. (2015), who found that years of education both before (i.e., early education) and after middle school (i.e., late education) was related to attenuated cognitive decline. Importantly, they found that the association between education and cognitive decline after middle school was mediated entirely by income. They proposed that early education promotes the development of critical skills, as well as cognitive and neural development in a sensitive period of childhood, which directly contribute to latelife protection against cognitive decline. In contrast, late education influences cognitive reserve indirectly by shaping employment opportunities and income, which contribute to latelife protection against cognitive decline by increasing access to quality health care and leisure opportunities, and reducing exposure to life stressors (Zahodne et al., 2015). For the historical periods relevant to our cohorts, differences in occupational and economic outcomes between High School and college graduates were relatively small (Baum, 2014; Taylor et al., 2014). This may therefore explain why the risk of cognitive impairment was comparable between those with a High School versus College education in our study.

The reduced risk of cognitive impairment associated with Elementary (vs. Incomplete Elementary education) and Middle (vs. Elementary) education weakened with older baseline age. Namely, both associations were significant in those aged 60, but not among those aged 80 years at baseline. Schmand et al. (1997) found that high versus low education was associated with significant reduction in the magnitude of cognitive decline among participants in the youngest (i.e., 65-70 years), but not in the oldest (i.e., 80+ years) age group. Similarly, Butler et al. found that holding a bachelor's degree was associated with a larger reduction in the amount of MMSE decline in nuns aged 75-84, compared to those aged 85+ at baseline(Butler et al., 1996). Interestingly, however, we found that High School (versus Elementary) education was associated with attenuated risk of cognitive impairment in both 60 *and* 80-year-old participants, which is broadly in line with the cognitive reserve hypothesis

(Meng and D'Arcy, 2012; Stern et al., 1999; Stern et al., 1992). Namely, in 80-year-olds, the level of neurodegeneration may have been so severe that lower levels of educational attainment (i.e., Elementary, and Middle) were insufficient to compensate for age-related cognitive deficits. However, having a High School education may have provided 80-year-olds with sufficient reserve to compensate for their higher degree of neurodegeneration, thus contributing to significant reductions in cognitive impairment risk relative to those with only Elementary education.

Some studies have found no moderating effect of baseline age on the relationship between education and cognitive decline. These studies, however, have used either very low cut-offs to define the younger and older-aged groups (i.e., 65 years) (Farmer et al., 1995), examined education solely as a continuous variable (Farmer et al., 1995; Van Dijk et al., 2008), or limited their analyses to linear associations(Van Dijk et al., 2008). On the other hand, not examining age as a moderator may explain why non-significant associations between education and cognitive decline were found in previous studies (Christensen et al., 2001; Seeman et al., 2005; Van Dijk et al., 2008; Winnock et al., 2002).

Overall, we found that the protective association between Middle education and cognitive impairment was significant in women but not men. Two previous studies examining sex differences found that low education was related to increased dementia risk in women but not men (Launer et al., 1999; Ott et al., 1999). Relatedly, an IPD meta-analysis found that leaving full-time education before versus after the age of 15 was associated with an increased risk of dementia death in women and not men (Russ et al., 2013). These sex differences have been attributed to larger socioeconomic discrepancies between those with low versus high education among women than men (Ott et al., 1999). Namely, women with low education are more likely to have worse occupational attainment, lower income, poorer health, fewer leisure opportunities, and consequently poorer cognitive outcomes than low educated men (Ott et al.,

1999; Sharp and Gatz, 2011). This is evident in Figure 1D, which indicated that the sex difference was primarily attributable to larger cognitive impairment among the Elementary (low) educated women than men.

Regarding ethnoregional differences, there was a larger difference in CI risk between the Elementary and High School education categories in Asians than Whites. Historically, in some Asian countries (e.g. Japan), those that received a High School education likely had better socioeconomic status than those who did not (Sorensen, 1994). In addition, educational systems in Hong Kong and South Korea were in disarray around the time of the Second World War (WWII), and illiteracy rates were high (Sorensen, 1994) implying that the quality of early education was poor in Asian countries during this period. Collectively, this suggests that the discrepancy between Elementary and High School education reflects wider gaps in educational quality and socioeconomic outcomes among Asians than Whites, hence leading to larger differences in cognitive performance between those with an Elementary versus High School education in Asians compared to Whites.

In contrast to Whites, in Blacks there was no significant reduction in CI risk associated with an Elementary (versus Incomplete Elementary) or Middle (versus Elementary) education, implying that early education was not protective in this group. This is possibly reflective of historical gaps in access to quality education between Blacks and Whites (Boozer et al., 1992; Carvalho et al., 2015), such that critical skills (e.g., reading, writing) were not adequately instilled among Blacks. Indeed, studies have found that differences in cognitive outcomes between Whites and Blacks are reduced after controlling for illiteracy (Carvalho et al., 2015; Sachs-Ericsson and Blazer, 2005). Interestingly, however, High School completion was associated with a significant reduction in CI risk among Blacks, and the size of this effect comparable to Whites. This aligns with Shadlen et al. (2006), who found that dementia incidence was significantly lower for Black Americans who had more (versus less) than 10

years of education. Fitzpatrick et al. (2004), however, found no significant differences in dementia incidence for Blacks with and without a High School education, although they didn't control for vascular risk factors or baseline cognition. Our results suggest that only late education reduced CI risk among Blacks. Hall et al. (2000) argued that, historically, for a Black American to attain an education beyond Middle school, they likely would have overcome economic deprivation, poverty, rural life, and acquired psychological resilience, collectively building their cognitive reserve, and thereby reducing their risk of cognitive impairment. We emphasise, however, that without access to relevant data, these proposed mechanisms are speculative at best.

Finally, we found no significant differences in the relationship between educational attainment and CI between *APOE*4* carriers and non-carriers. Results showed, however, that only High School attainment was related to reduced CI risk in *APOE*4* carriers, implying that a higher degree of cognitive reserve is needed to counteract faster cognitive decline associated with *APOE*4*. Similarly, Shadlen et al. (2005) found that there were greater reductions in the magnitude of cognitive decline in *APOE*4* homozygotes with increasing years of education. Our ethnoregional analyses, however, indicated that High School completion was related to a reduced risk of cognitive impairment (relative to Elementary school) in Asian and Black, but not White, *APOE*4* carriers. Furthermore, Middle education was related to decreased CI risk in Asian *APOE*4* carriers. As discussed above, differences between lower and higher levels of education, in particular completing versus not completing High School, may reflect wider gaps in socioeconomic status (Hall et al., 2000; Sharp and Gatz, 2011), literacy (Sachs-Ericsson and Blazer, 2005), occupational complexity (Andel et al., 2006), income (Zahodne et al., 2015), and health outcomes (Williams et al., 2016) in Asians and Blacks than in Whites. Each of these factors is associated with reduced dementia incidence (Andel et al., 2006; Russ et al., 2013; Sharp and Gatz, 2011). This implies that higher educational attainment is

correlated with larger reductions in *multiple* dementia risk factors in Blacks and Asians compared to Whites. Consequently, this may explain why High School attainment was associated with significant attenuation of CI risk in Asian and Black, but not White *APOE*4* carriers. Interestingly, Elementary versus Incomplete Elementary education was related to reduced CI risk in White *APOE*4* carriers only. We speculate that poor-quality Elementary Education available to Asians and Blacks in previous decades may not have built a sufficient level of cognitive reserve to overcome *APOE*4*-mediated cognitive impairments in these ethnic groups.

Because of limited access to relevant data, it is not possible for us to disentangle whether the reductions in cognitive impairment are primarily due to cognitive reserve or other variables that education is a proxy for (e.g., income, socioeconomic status, access to healthcare). This also precludes our ability to investigate more complex research questions, including the factors that mediate reductions in CI risk associated with education. We were also not able to control for literacy levels, which may (in part) account for the observed ethnic, gender, and age (and/or cohort) differences in the relationship between education and cognitive impairment. Our study is, however, strengthened by our large and diverse sample; our ability to control for several possible confounders/vascular risk factors; use of inverse probability weighting to reduce bias in parameter estimates due to non-random attrition; and the availability of educational IPD, enabling us to classify participants into finer-grained, educational categories. The cut-offs used to classify participants into these levels of achievement, furthermore, were tailored to the specific educational system of that country, thus enhancing the generalisability of our findings.

In this IPD meta-analysis of 18 population-based studies, we found that compared to Elementary education, attainment of a Middle or High School education was related to significant reduction in the risk of cognitive impairment. There was, however, no difference

in CI risk between those with a complete High School or Tertiary education. The decreased CI risk associated with Middle education weakened with older baseline age and was stronger in women than men. The reduced risk of CI associated with High School completion, however, was unrelated to sex or baseline age, but emerged stronger in Asians than Whites. Finally, High School completion was related to reduced CI risk in *APOE*4* carriers, specifically among those of Asian and Black ethnicity. High School completion may potentially reduce the risk of CI associated with advancing age and carriage of *APOE*4* among non-White ethnic groups. The emergent ethnic differences may be attributable to historically wider gaps in socioeconomic status, employment opportunities, income, and health between low and high educated individuals in Asian and Black, versus White populations. Limited access to this data precludes us from making definitive conclusions about ethnic differences in how education influences the trajectory of cognitive decline in late adulthood. This limitation points to the challenges of studying ethnic differences in cognitive ageing, particularly in relation to examining differential impacts of risk and protective factors between and within ethnic groups (Brewster et al., 2019). A complete and unbiased analysis of risk factors take into account ethnoregional differences in genetics (e.g., ethnicity-specific genetic risk factors for Alzheimer's Disease), biology, early life deprivation, neighbourhood characteristics (e.g., economically disadvantaged, ethnically homogenous), social and political history (e.g., experiences of discrimination and policies promoting inequality), health outcomes (e.g., vulnerability to cerebrovascular risk factors), income and employment across the lifespan, attitudes to the care of older adults with dementia (e.g., nursing home versus family care) and a wide range of other factors (Glymour and Manly, 2008). Historically, however, studies of normative ageing have been limited to non-Latino white participants, and therefore access to this rich data has been limited. Furthermore, cognitive tests used to inform

dementia diagnoses are sensitive to educational attainment adding further complexity to unbiased assessment of cognitive decline across ethnic groups (Glymour and Manly, 2008).

Besides data and measurement limitations, the consideration of complex social, political, and biological factors and how they interact with risk and protective factors (e.g., education) of cognitive ageing calls for the greater use of *complex systems models*, where interrelations and interactions among multiple levels of relevant variables can be modelled (Brewster et al., 2019). Here the impact of risk factors on cognitive outcomes can be examined in the context of a complex interplay of biological, clinical, political, and social factors. Such models have been used to examine determinants of racial and ethnic disparities in obesity and HIV transmission, and their application to cognitive ageing provides a promising avenue for future research.

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FIGURE LEGENDS

Figure 1. Relationship between education and risk of cognitive impairment (i.e., MMSE ≤ 23).A) Proportion of participants cognitively unimpaired over time for participants in each of the educational attainment categories. B) Proportion of cognitively unimpaired participants aged 60 and 80 years at baseline with either an Incomplete Elementary, Elementary, or High School education. C) Proportion of cognitively unimpaired men and women at baseline with either an Elementary or Middle education.

Figure 2. Ethnoregional differences in risk of cognitive impairment between education groups. A) Proportion of cognitively unimpaired White and Asian participants with an Elementary or High School education. B) Proportion of cognitively unimpaired White and Black participants with an Elementary or High School education

Figure 3. Interaction between educational level and carriage of *APOE*4* on the risk of cognitive impairment in ethnoregional groups. A) Proportion of cognitively unimpaired Asian *APOE*4* carriers and non-carriers with an Elementary or Middle education. B) Proportion of cognitively unimpaired White *APOE*4* carriers and non-carriers with an Elementary or Middle education. C) Proportion of cognitively unimpaired Black *APOE*4* carriers and non-carriers with an Elementary or High School education. D) Proportion of cognitively unimpaired White *APOE*4* carriers and non-carriers with an Elementary or High School education. Abbreviations: C, *APOE*4* carriers; NC, *APOE*4* non-carriers.

Table 1. *Descriptive Statistics of Each Included Study at Baseline*

				Sex			Education					Covariates					Ethnicity				
	N	Lost to follow up	Impaired	Female	Age, y	Follow up, y	Education, y	Incomplete Elementary	Elementary	Middle Level	High School	CVD	DIAB	HT	Stroke	*APOE *4* carrier	White	Asian	Black	Other	Missing
Study	Analysed[a]	(%)	N (%)	%	M (SD)	M (SD)	M (SD)	%[b]	%	%	%	%	%	%	%	%	%	%	%	%	%
BAMBUI[c]	1329	72.4	827 (62.2)	62.4	68.6 (6.9)	10.1 (4.7)	2.9 (3)	88.1	5.3	4.2	2	15.5	14.8	68.2	3.5	25.2	60.7		2.3	36.9	
CAS	1464	0	222 (15.2)	66.0	73.7 (6.4)	4.6 (0.9)	9.5 (4.7)	21.8	32.2	-	46	29.5	31.8	75.7	6.0	16.7	67.9		16.3	10.4	5.4
CFAS	8253	63.2	1951 (23.6)	58.6	74.3 (6.4)	4.9 (3.8)	10.1 (2.3)	0.7	5.4	65.5	28.5	17.3	5.5	32.5	5.9	24.0	64.7		0.2	0.1	35.0
EAS	1220	99.8	220 (18)	61.6	78.1 (5.4)	4.4 (3.3)	13.6 (3.5)	0.4	3.5	16.6	79.5	33.7	16.2	63.9	9.0	22.2	68.5	0.4	27.1	3.9	
ESPRIT[d]	1916	36.3	220 (11.5)	59.3	72.9 (5.4)	6 (2.3)	10.4 (3.7)	23.4	18.2	10.7	47.7	19.5	8.8	71.4	3.2	19.3	100.0				
HELIAD[d]	419	0	69 (16.5)	59.2	71.9 (5.8)	2.8 (0.6)	6.3 (3.2)	23.4	60.9	3.1	12.6	21.0	15.8	64.9	6.9	17.2	100.0				
HK-MAPS[d]	561	24.4	169 (30.1)	54.4	72 (7)	4.6 (1.5)	5 (4.7)	55.4	19.6	10	15	16.4	18.2	49.9	7.3	13.3		100.0			
Invece.Ab[d]	977	0	32 (3.3)	52.6	72.1 (1.3)	2.2 (0.2)	7.1 (3.3)	7.2	51.1	31.7	10	27.3	18.0	60.6	7.6	18.4	100.0				
KLOSCAD[d]	4331	0	787 (18.2)	56.3	69.3 (6.2)	2 (0.3)	8.7 (5.3)	21.4	25.9	13.3	39.4	13.2	26.9	61.2	9.4	25.4		100.0			
LEILA[d]	766	93.6	208 (27.2)	73.4	81.1 (4.6)	5.4 (3.3)	12 (1.8)			21.5	78.3	8.1	22.8	81.7	6.5	16.0	100.0				
MoVIES	368	83.2	201 (54.6)	49.2	74.6 (6.1)	7.9 (4.1)	10.6 (2.7)	1.4	33.7	16	48.9	41.3	14.1	70.4	9.2	25.1	96.7		3.3		
PATH	2212	13.5	44 (2)	48.4	62.5 (1.5)	7.5 (1.4)	13.9 (2.7)	0.8	10.1	35.4	53.8	14.8	7.1	65.7	3.9	27.1	96.1	2.4		0.0	1.5
SALSA[d]	1438	47.1	359 (25)	58.3	70.1 (6.6)	6.3 (2.4)	7.6 (5.4)	33.4	17	17.5	32.1	22.2	31.4	67.5	8.2	14.2				100.0	
SGS[d]	842	0	47 (5.6)	57.2	72.8 (5.6)	2 (0)	11.4 (2.6)	0.5	8.1	36.5	55	12.4	12.7	37.2	3.3	b		100.0			
SLASI[d]	432	44.2	41 (9.5)	62.5	64.7 (6.7)	2.9 (1.2)	7 (4.4)	32.1	21	9.6	37.3	10.0	12.8	60.7	3.0	16.6		100.0			
SydneyMAS	891	25.5	76 (8.5)	54.3	78.5 (4.7)	5.2 (1.4)	11.7 (3.5)	2.1	42.6	20.1	35.1	28.5	15.3	82.9	3.9	22.7	98.0	1.0			1.0
ZARADEMP	3161	25.3	521 (16.5)	55.5	71.9 (8.7)	4.1 (1.2)	7.6 (3.9)	41.5	40.2	3.7	14.6	6.7	12.3	67.8	4.8	b	100.0				
Tajiri[c]	98	0	18 (18.4)	57.1	71.1 (3.9)	5 (0)	8.1 (1.8)	5.1	76.5	13.3	5.1	2.0	10.2	71.4	0	b		100.0			

Abbreviations: APOE*4, Apolipoprotein E ε4; Bambui, Bambui Cohort Study of Aging; CHAS, Cuban Health and Alzheimer Study; CVD, cardiovascular disease history; DIAB, diabetes, EAS, Einstein Aging Study; ESPRIT, Etude Santé Psychologique et Traitement; HELIAD, Hellenic Longitudinal Investigation of Aging and Diet; HK-MAPS, Hong Kong Memory and Ageing Prospective Study; HT, hypertension; Invece.Ab, Invecchiamento Cerebrale in Abbiategrasso; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; LEILA75+, Leipzig Longitudinal Study of the Aged; MoVIES, Monongahela Valley Independent Elders Survey; PATH, Personality and Total Health

Through Life Project; SALSA, Sacramento Area Latino Study on Aging; SGS, Sasaguri Genkimon Study; SLASI, Singapore Longitudinal Ageing Studies; SydneyMAS, Sydney Memory and Ageing Study; ZARADEMP, Zaragoza Dementia Depression Project.

[a] Refers to the number of participants used in survival analysis. This includes participants with data for age at baseline, sex, education, all covariates, and have valid time-to-event information. Participants that dropped out at the initial wave are excluded from survival analyses because no time to event information is available

[b] Values in percentages are in relation to analysed sample (i.e., those with time-to-event information). Percentages may sum to less or more than 100 due to rounding error. Current smoking and high cholesterol were not used as covariates in the analysis as data for these variables was not available in all studies (Bambui did not have data on individuals who were non-smokers, and the KLOSCAD, LEILA, and MoVIES studies lacked data on high cholesterol).

[c] Data relating to ethnicity in the Bambui study derived from a variable coding the skin colour of participants. For the purposes of ethnoregional analyses, however, the ethnicity of all participants in Bambui was regarded as Brazilian, as advised by the chief investigators of this study, and consequently all participants in this study were excluded from comparisons between Whites and Asians.

[d] IPD for ethnicity was not available in these studies. Participants were assigned to the majority ethnic group of the study sample based on the recommendations of each study's lead investigator(s).

Table 2. *Results of Parametric Survival Analysis Examining Association Between Education and Risk of Cognitive Impairment and Moderation by Age, Sex, and APOE*4*

	HR (95% confidence interval)	**P**
Continuous		
Education	0.881, (0.847-0.916)	0.000
Education x Age	1.006, (1.003-1.01)	0.000
Education effect at 80 y	0.94, (0.913-0.968)	0.000
Education effect at 60 y	0.826, (0.773-0.883)	0.000
Education^2	1.003, (1-1.006)	0.031
Education^2 x Age	0.999, (0.999-1)	0.002
Education^2 effect at 80 y	0.997, (0.991-1.004)	0.409
Education^2 effect at 60 y	1.009, (1.007-1.012)	0.000
Education x Sex	1.026, (0.997-1.055)	0.074
Education^2 x Sex	1.001, (0.995-1.008)	0.743
Categorical		
Incomplete Elementary	1.645 (1.324-2.045)	0.000
Incomplete Elementary x Age	0.955 (0.933-0.978)	0.000
Old	1.041 (0.771-1.406)	0.794
Young	2.601 (1.854-3.648)	0.000
Incomplete Elementary x Sex	1.002 (0.754-1.33)	0.991
Female	1.625 (1.328-1.988)	0.000
Male	1.627 (1.163-2.277)	0.005
Middle Level	0.645 (0.479-0.87)	0.004
Middle Level x Age	1.038 (1.009-1.067)	0.009
Old	0.937 (0.765-1.147)	0.527
Young	0.444 (0.259-0.763)	0.003
Middle Level x Sex	1.309 (1.109-1.545)	0.001
Female	0.58 (0.438-0.769)	0.000
Male	0.76 (0.533-1.083)	0.128
High School	0.472 (0.312-0.715)	0.000
High School x Age	1.029 (0.999-1.061)	0.056
Old	0.631 (0.489-0.815)	0.000
Young	0.353 (0.18-0.694)	0.003
High School x Sex	1.215 (0.968-1.525)	0.093
Female	0.437 (0.296-0.643)	0.000
Male	0.53 (0.326-0.862)	0.011
High School versus Middle Level	0.732 (0.599-0.894)	0.002
College versus High School (some College)	0.762 (0.487-1.192)	0.234
College v Middle	0.595 (0.345-1.026)	0.062
College v Elementary	0.381 (0.184-0.788)	0.009
Education and *APOE*4*		

Incomplete Elementary		
APOE*4 x Incomplete Elementary	0.906 (0.66-1.244)	0.543
Incomplete Elementary (NC)	1.526 (1.226-1.901)	0.000
Incomplete Elementary (C)	1.383 (0.953-2.008)	0.088
APOE*4 x Incomplete Elementary x Age	0.998 (0.956-1.04)	0.910
APOE*4 x Incomplete Elementary x Sex	0.928 (0.602-1.432)	0.737
Middle		
APOE*4 x Middle	1.505 (0.946-2.394)	0.084
Middle (NC)	0.496 (0.316-0.78)	0.002
Middle (C)	0.747 (0.454-1.229)	0.251
APOE*4 x Middle x Age	0.977 (0.929-1.027)	0.355
APOE*4 x Middle x Sex	0.961 (0.577-1.6)	0.879
High School		
APOE*4 x High School	1.002 (0.62-1.619)	0.994
High School (NC)	0.519 (0.316-0.851)	0.009
High School (C)	0.52 (0.324-0.834)	0.007
APOE*4 x High School x Age	1.014 (0.973-1.058)	0.505
APOE*4 x High School x Sex	1.458 (0.868-2.45)	0.154

Abbreviations: APOE*4, Apolipoprotein E ε4; C, APOE*4 carrier; NC, APOE*4 non-carrier;

Table 3. *Ethnicity Differences in the Association Between Education and Risk of Cognitive Impairment, and oderation by Age and APOE*4.*

	Asians		**Blacks**		**Whites**	
	HR (95% confidence interval)	**p**	**HR (95% confidence interval)**	**p**	**HR (95% confidence interval)**	**p**
Education						
Incomplete Elementary						
Incomplete Elementary x Ethnicity	0.87 (0.676-1.119)	0.278	0.866 (0.431-1.743)	0.688	1[a]	
Within Ethnic Group: Incomplete Elementary	1.631 (1.535-1.734)	0.000	1.625 (0.768-3.437)	0.204	1.875 (1.454-2.418)	0.000
Incomplete Elementary x Age	0.977 (0.942-1.013)	0.208	0.993 (0.908-1.087)	0.879	1[a]	
Within Ethnic Group: Incomplete Elementary x Age	0.943 (0.911-0.977)	0.001	0.959 (0.88-1.045)	0.341	0.966 (0.954-0.978)	0.000
Middle						
Middle Level x Ethnicity	0.984 (0.675-1.434)	0.934	1.664 (0.759-3.649)	0.204	1[a]	
Within Ethnic Group: Middle	0.595 (0.405-0.875)	0.008	1.006 (0.443-2.287)	0.988	0.605 (0.507-0.721)	0.000
Middle Level x Age x Ethnicity	0.972 (0.944-1.001)	0.058	1.014 (0.887-1.16)	0.837	1[a]	
Within Ethnic Group: Middle x Age	1.015 (0.996-1.035)	0.121	1.059 (0.927-1.211)	0.399	1.044 (1.018-1.072)	0.001
High School						
High School x Ethnicity	0.575 (0.406-0.815)	0.002	0.909 (0.573-1.442)	0.685	1[a]	
Within Ethnic Group: High School	0.29 (0.238-0.354)	0.000	0.459 (0.287-0.734)	0.001	0.505 (0.363-0.704)	0.000
High School x Age x Ethnicity	1.047 (1.001-1.094)	0.044	1.002 (0.925-1.085)	0.968	1[a]	
Within Ethnic Group: High School x Age	1.078 (1.038-1.12)	0.000	1.032 (0.959-1.11)	0.404	1.03 (1.008-1.052)	0.007
Education and *APOE*4*						
Incomplete Elementary						
APOE x Incomplete Elementary x Ethnicity	0.555 (0.34-0.905)	0.018	[b]		1[a]	
Within ethnicity: APOE*4 x Incomplete Elementary	0.725 (0.496-1.06)	0.097	[b]		1.306 (0.854-1.997)	0.217
Incomplete Elementary (NC)	1.572 (1.161-2.129)	0.003	[b]		1.834 (1.269-2.65)	0.001
Incomplete Elementary (C)	1.139 (0.669-1.939)	0.631	[b]		2.395 (1.325-4.329)	0.004
Middle Level						
APOE x Middle x Ethnicity	0.304 (0.182-0.507)	0.000	1.039 (0.683-1.58)	0.859	1[a]	-
Within Ethnicity: APOE*4 x Middle Level	0.69 (0.505-0.943)	0.020	2.366 (1.435-3.901)	0.001	2.271 (1.457-3.538)	0.000
Middle (NC)	0.493 (0.403-0.602)	0.000	0.634 (0.295-1.362)	0.243	0.382 (0.275-0.529)	0.000
Middle (C)	0.34 (0.257-0.449)	0.000	1.5 (0.957-2.352)	0.077	0.867 (0.545-1.379)	0.547
High School						
APOE*4 x High School x Ethnicity	0.636 (0.362-1.118)	0.116	0.731 (0.316-1.692)	0.465	1[a]	
Within Ethnicity: APOE x High School	0.896 (0.676-1.187)	0.444	0.83 (0.322-2.138)	0.700	1.408 (0.804-2.466)	0.231
High School (NC)	0.27 (0.182-0.4)	0.000	0.461 (0.16-1.324)	0.150	0.448 (0.268-0.751)	0.002
High School (C)	0.242 (0.204-0.287)	0.000	0.382 (0.175-0.834)	0.016	0.632 (0.349-1.143)	0.129

Abbreviations: APOE*4, Apolipoprotein E ε4; C, APOE*4 carrier; NC, APOE*4 non-carrier;

[a] Reference Group

[b] Because of the small numbers of Black APOE*4 carriers in the low education groups, the Elementary and Incomplete Elementary groups were collapsed and treated as the reference education group.

Supplementary Tables

eTable 1. Information Relating to all Twenty Participating COSMIC Studies

Study	Abbreviation	Location	Main race/ethnicity	Sample size	Years run	Reference
Bambui Cohort Study of Aging	Bambui	Bambui, Brazil	Brazilian	1491	1997–2013	Lima-Costa et al. (2011)
Cognitive Function & Ageing Study	CFAS	United Kingdom†	White	12256	1989–	Brayne et al. (2006)
Cuban Health and Alzheimer Study	CHAS	Havana and Matanzas, Cuba	White, Black, Mixed	2574	2003–	Llibre-Rodriguez et al. (2017)
Einstein Aging Study	EAS	New York, USA	White, Black	2063	1993–	Katz et al. (2012)
Etude Santé Psychologique et Traitement	ESPRIT	Montpellier, France	White	2187	1999–	Ritchie et al. (2010)
Hellenic Longitudinal Investigation of Aging and Diet	HELIAD	Larissa and Marousi, Greece	White	1174	2010–	Dardiotis et al. (2014)
Hong Kong Memory and Ageing Prospective Study	HK-MAPS	Hong Kong	Chinese	785	2005–	Sachdev et al. (2013)
Invecchiamento Cerebrale in Abbiategrasso	Invece.Ab	Abbiategrasso, Italy	White	1267	2010–2015	Guaita et al. (2013)
Korean Longitudinal Study on Cognitive Aging and Dementia	KLOSCAD	South Korea (nation-wide)	Korean	6513	2009–	Han et al. (2018)
Leipzig Longitudinal Study of the Aged	LEILA75+	Leipzig, Germany	White	1040	1997–2014	Riedel-Heller et al. (2001)
Monongahela Valley Independent Elders Survey	MoVIES	Mid-Monongahela Valley, PA, USA	White	1613	1987–2002	Ganguli et al. (2000)
Personality and Total Health Through Life Project	PATH	Canberra, Australia	White	2545	2001–	Anstey et al. (2012)
Sacramento Area Latino Study on Aging	SALSA	Sacramento Valley, CA, USA	Hispanic; Mexican ancestry	1710	1998–2008	Haan et al. (2003)
Sasaguri Genkimon Study	SGS	Sasaguri, Japan	Japanese	793	2011–	Narazaki et al. (2013)
Singapore Longitudinal Ageing Studies (I)	SLASI	Singapore	Chinese	1858	2003–	Feng et al. (2010)
Sydney Memory and Ageing Study	Sydney MAS	Sydney, Australia	White	1037	2005–	Sachdev et al. (2010)

Tajiri Project	Tajiri	Tajiri, Japan	Japanese	100	1998–2005	Meguro et al. (2007)
Zaragoza Dementia Depression Project	ZARADEMP	Zaragoza, Spain	White	4542	1994–	Lobo et al. (2005)

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eTable 2. 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	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	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	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(Crane et al., 2008)	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(Thal et al., 1986).	1. Blood pressure (mean of 2) 2. History	Myocardial infarction, coronary artery bypass, angina, heart failure, angioplasty, or arrhythmia	1. History 2. Treatment 3. Fasting blood glucose	Medical history of stroke

Study	Criteria used to classify dementia	General Cognition test	Hypertension[a]	Cardiovascular disease[b]	Diabetes[c]	Stroke[d]
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	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 or 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	History	Coronary disease, myocardial infarction, congestive heart failure, arrhythmia, or any other heart disease	History	Medical history of stroke or TIA
HK-MAPS	Clinical Dementia Rating ≥1	MMSE	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 severity rating 1+ for cerebrovascular disease (CVA, TIA)
Invece.Ab	DSM-IV	MMSE	1. Medication 2. Supine blood pressure 170-180 mmHg and history	1. Cardiovascular disease defined by study as any of myocardial infarction, heart failure, angina, arrhythmia,	1. Treatment 2. History	History of stroke or TIA

Study	Criteria used to classify dementia	General Cognition test	Hypertension[a]	Cardiovascular disease[b]	Diabetes[c]	Stroke[d]
			3. Supine blood pressure >180 mmHg	coronary artery bypass graft, or other 2. Medication 3. Atrial fibrillation		
KLOSCAD	DSM-IV	MMSE	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 indicated 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	1.Blood pressure	Self-reported myocardial infarction	Self-reported	Self-reported history of stroke
MoVIES	Clinical Dementia Rating ≥1	MMSE	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 assessed at wave 2 indicating presence >1 month ago)
PATH	DSM-IV	MMSE	1. Blood pressure (mean of 2) 2. Medication	"Do you have heart trouble?"	1. History 2. Treatment	"Have you ever suffered a stroke?"

Study	Criteria used to classify dementia	General Cognition test	Hypertension[a]	Cardiovascular disease[b]	Diabetes[c]	Stroke[d]
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(Crane et al., 2008)	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
SGS	Self-reported medical history	MMSE	Self-reported history of diagnosis	Self-reported history of diagnosis	Self-reported history of diagnosis	Self-reported history of diagnosis
SLASI	DSM-IV	MMSE	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	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
Tajiri	Clinical Dementia Rating ≥1, with DSM-IV follow-up	MMSE	1. Blood pressure (mean of 2) 2. Medication	Ischemic heart disease, or atrial fibrillation	1. Fasting blood glucose 2. Treatment (diet)	Medical history
ZARADEMP	DSM-IV	MMSE	Diagnosis using EURODEM Risk Factor Questionnaire and medical records	Diagnosis of myocardial infarction or angina using EURODEM Risk Factor Questionnaire and medical records	Diagnosis using EURODEM Risk Factor Questionnaire and medical records	History 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.

eTable 3. 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 (ΒΕΥ846Ψ8Ν2-32Π)
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)
SGS	Institutional Review Board of the Institute of Health Science, Kyushu University (IHS-2010-22)
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)
Tajiri	Ethical Committee of Tohoku University Graduate School of Medicine (#2012276, #2014160, #20141238, and #20141767)
ZARADEMP	Ethics committee of the Zaragoza University Hospital (CEICA # CP16/2012)

Written consent was exclusively or predominantly obtained from participants in all studies (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).

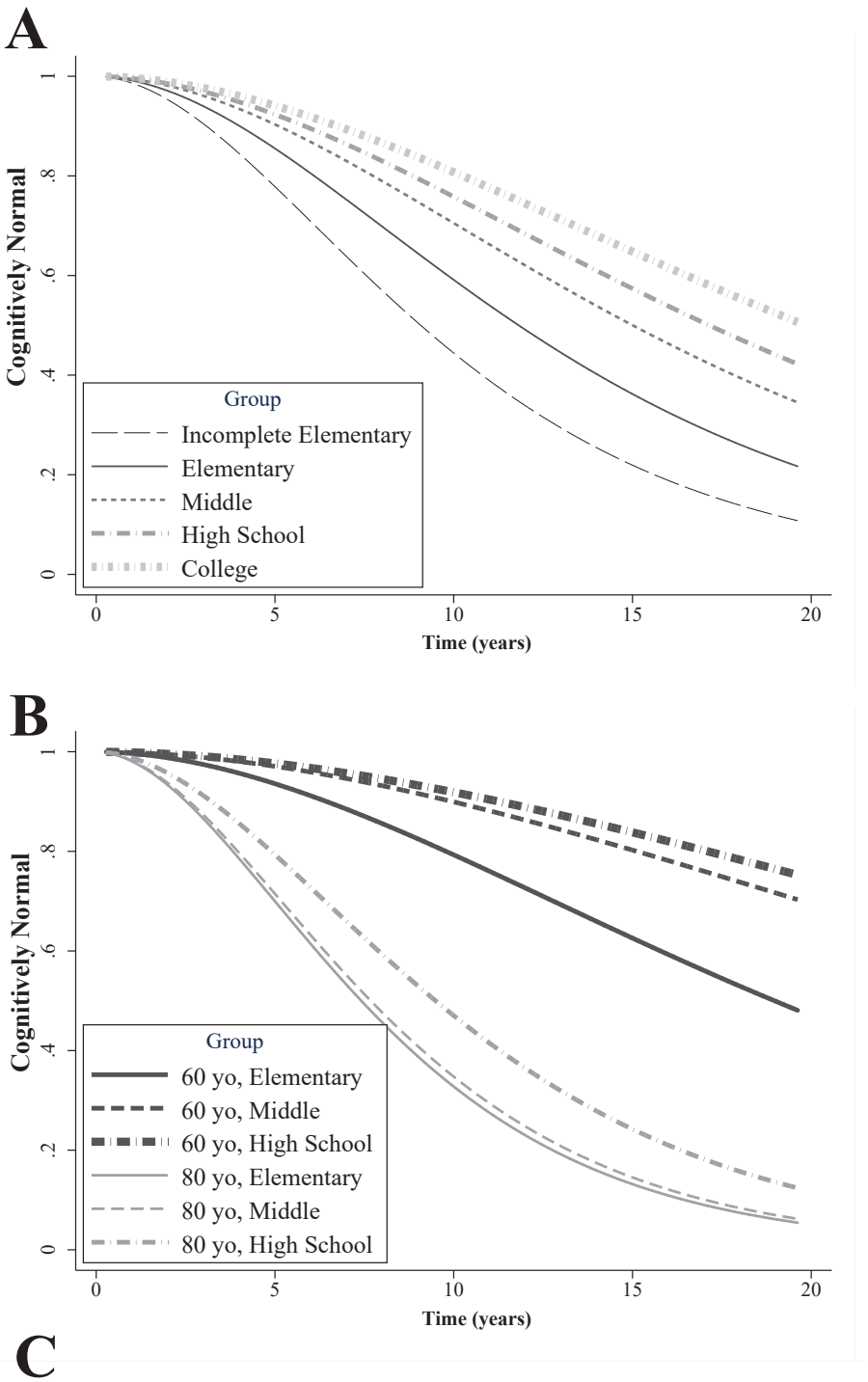
eTable 4 – Harmonization of Educational Attainment Across Cohorts

			Assigned Educational Category			
Country	**Study**		**Incomplete Elementary**	**Completed Elementary (and incomplete Middle Level)**	**Completed Middle (and some High School)**	**Completed High School (may or may not have completed Tertiary)**
Brazil		**Education System**	**Less than 5 years**	**5 to <9 years**	**9 to <12 years**	**12+ years**
	Bambui	**Available categories**	Illiterate; 1-3 years, 4-7 years	>=8 years	>=8 years	>=8 years
		Education in Years[a]		Available. Year data used to assign participants to these higher categories		
United Kingdom		**Education System**	**Less than <6 years**	**6 to <9 years**	**9 to <11 years**	**11+ years**
	CFAS	**Available categories**	None.			
		Education in Years	Available. Year data used to assign participants to a specific level of educational attainment using the Education System information			
Cuba		**Educational System**	**Less than 6 years**	**6 to <9 years**	**9 to <12 years**	**12+ years**
	CHAS	**Available categories**	None; Some, did not complete primary	Completed Primary	Completed Primary	Completed Secondary; Tertiary
		Education in Years		Available. Year data used to assign participants into either Complete Elementary or Complete Middle categories		
USA		**Educational System**	**Less than 5 years**	**5 to <8 years**	**8 to <12**	**12+ years**
	EAS	**Available categories**	*No categorical data applicable to these levels of education*			High School Diploma/GED Bachelors; Masters; Doctorate; Other
		Education in Years	Available. Year data used to assign participants to these levels of educational attainment			
	MOVIES	**Available categories**	<6th grade	6-9th grade	Partial high school	High School Graduate; Trade/Technical, Partial College College Graduate; Graduate/Professional
		Education in Years	Available. Used to assign participants to a level of educational attainment if categorical data missing			
	SALSA	**Available categories**	None.			
		Education in years	Available. Used to assign participants to a specific level of educational attainment using the Education System information			
France		**Educational System**	**Less than 5 years**	**5 to <9 years**	**9 to <12 years**	**12+ years**
	ESPRIT	**Available categories**	<5th Grade	5th Grade; 6th To 9th Grade	Technical 9th Grade;	College; College Graduate (including Technical); University
		Education in Years	Not available.			
Greece	**HELIAD**	**Educational System**	**Less than 5 years**	**5 to <9 years**	**9 to <12 years**	**12+ years**
HELIAD		**Available categories**	None.			
		Education in Years	Available. Used to assign participants to a specific level of educational attainment using the Education System information			
Hong Kong	**HK-MAPS**	**Educational System**	**Less than 6 years**	**6 to <9 years**	**9 to <11 years**	**11+ years**
		Available categories	None.			
		Education in Years	Available. Used to assign participants to a specific level of educational attainment using the Education System information			
Italy		**Educational System**	**Less than 5 years**	**5 to <8 years**	**8 to <13 years**	**13+ years**
	Invece.Ab	**Available categories**	None.			
		Education in Years	Available. Used to assign participants to a specific level of educational attainment using the Education System information			

South Korea	**KLOSCAD**	**Educational System**	**Less than 6 years**	**6 to <9 years**	**9 to <12 years**	**12+ years**
		Available Categories	Less Than High School Completion	Less Than High School Completion	Less Than High School Completion	High School Completion; University Degree
		Education in Years	Available. Used to assign participants into a level educational attainment below High School			
Germany		**Educational System**	**Less than 4 years**	**4 to <9 years**	**9 to <12 years**	**12+ years**
	LEILA	**Available Categories**	*No categorical data applicable to these levels of education*		Lower Secondary Education	Upper Secondary Education; Post-Secondary Non-Tertiary; Short Cycle Tertiary Education; Master Or Equivalent; Doctoral or Equivalent
		Education in Years	Available. Used to assign participants into a level educational attainment below Middle education			
Australia		**Educational System**	**Less than 7 years**	**7 to <11 years**	**11 to <13 years**	**13+ years**
	PATH	**Available Categories (PATH)**	Some Primary	All Of Primary, Some Of Secondary	Intermediate School Certificate	Five/Six Years of Secondary: Trade Certificate/Apprenticeship; Technicians Certificate/Advanced Certificate; Certificate Other Than Above; Associate Diploma; Undergraduate Diploma; Bachelor's Degree; Post Graduate Diploma/Certificate; Higher Degree;
		Education in Years	Available. Used to assign participants to a level of educational attainment if categorical data missing.			
	MAS	**Available Categories**	*No categorical data applicable to this category.*	Primary school, Incomplete High School	Incomplete High School; Incomplete High School + Certificate Diploma	Complete High School; Incomplete Tertiary; Complete High School + Certificate/Diploma; Completed Tertiary
		Education in Years	Available. Used to categorize participants with incomplete Elementary education			
Japan		**Educational System**	**Less than 6 years**	**6 to <9 years**	**9 to <12**	**12+ years**
	Tajiri	**Available Categories**	Less Than High School	Less Than High School	Less Than High School	High School
		Education in Years	Available. Used to assign participants to a specific level of educational attainment below High School			
	SGS	**Available Categories**	None.			
			Available. Used to assign participants to a specific level of educational attainment using the Education System information			
Singapore		**Educational System**	**Less than 6 years**	**6 to <8 years**	**8 to <10**	**10+ years**
		Available Categories	Less Than High School Completion	Less Than High School Completion	Less Than High School Completion	High School Completion, Technical or College Diploma; University Level
		Education in Years		Available. Used to assign participants to either Elementary of Middle education		
Spain		**Educational System**	**Less than 6 years**	**6 to <8 years**	**8 to < 10 years**	**10+ years**
		Available Categories (ZARADEMP)	None; Less Than Primary	Primary	Less Than High School	High School; College Diploma; Less Than Technical Formation; University Degree
		Education in Years	Available. Used to assign participants to a level of educational attainment if categorical data missing			

[a] For all studies, the year data was used to assign participants to the relevant level of educational attainment if categorical data was not available, or was not at a level of detail to assign participants to one of the four educational attainment categories.

Figure 1


A
Cognitively Normal
0
.2
.4
.6
.8
1
0
5
10
15
20
Time (years)
Group
Incomplete Elementary
Elementary
Middle
High School
College

B
Cognitively Normal
0
.2
.4
.6
.8
1
0
5
10
15
20
Time (years)
Group
60 yo, Elementary
60 yo, Middle
60 yo, High School
80 yo, Elementary
80 yo, Middle
80 yo, High School

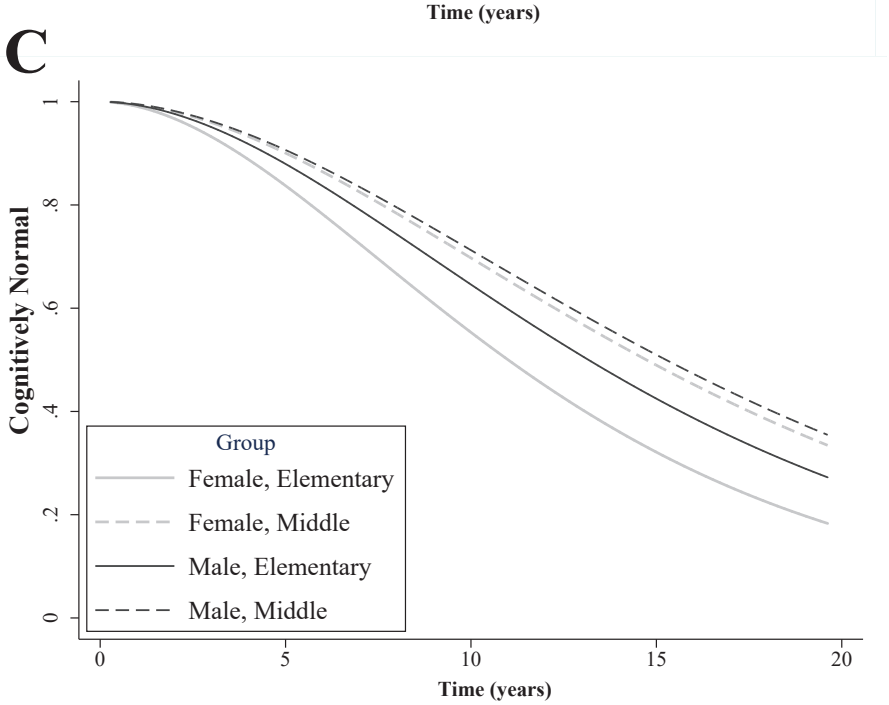

C
Cognitively Normal
0
.2
.4
.6
.8
1
0
5
10
15
20
Time (years)
Group
Female, Elementary
Female, Middle
Male, Elementary
Male, Middle

Figure 2

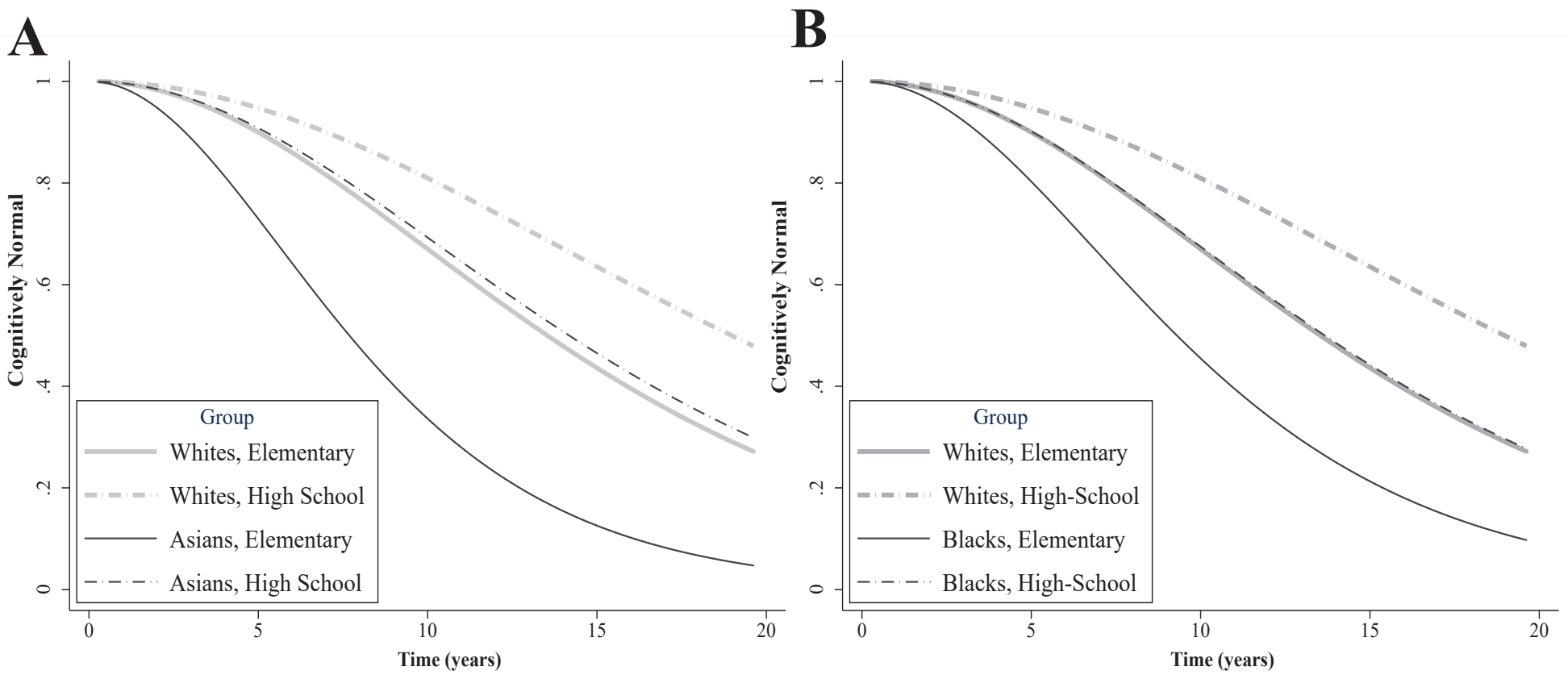
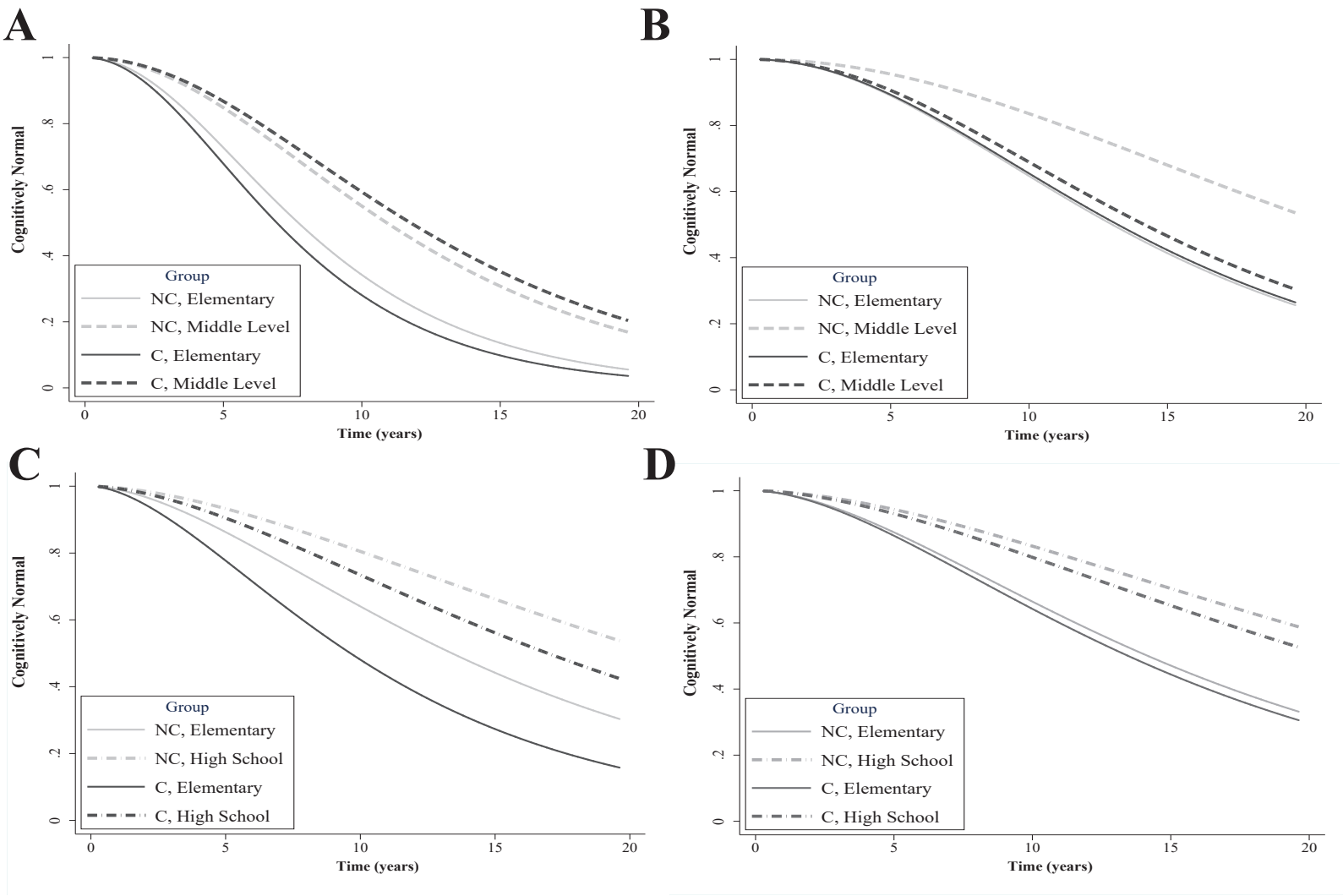

A
Cognitively Normal
0
.2
.4
.6
.8
1
0
5
10
15
20
Time (years)
Group
Whites, Elementary
Whites, High School
Asians, Elementary
Asians, High School
B
Cognitively Normal
0
.2
.4
.6
.8
1
0
5
10
15
20
Time (years)
Group
Whites, Elementary
Whites, High-School
Blacks, Elementary
Blacks, High-School

Figure 3


A
B
C
D
Cognitively Normal
Time (years)
0
5
10
15
20
.2
.4
.6
.8
1
Group
NC, Elementary
NC, Middle Level
C, Elementary
C, Middle Level
NC, High School
C, High School

Abstract

Background:

We examined how the relationship between education and latelife cognitive impairment (defined as a Mini Mental State Examination score ~~less than~~below 24) is influenced by age, sex, ethnicity, and Apolipoprotein E epsilon 4 (*APOE*4*).

Methods

Participants were 30,785 dementia-free individuals aged 55-103 years, from 18 longitudinal cohort studies, with an average follow-up ranging between 2 and ~~and~~ 10 years. Pooled hazard ratios were obtained from multilevel parametric survival analyses predicting cognitive impairment (CI) from education and its interactions with baseline age, sex, *APOE*4* and ethnicity. In separate models, education was treated as continuous (years) and categorical, with participants assigned to one of four education completion levels: Incomplete Elementary; Elementary; Middle; and High School.

Results

Compared to Elementary, Middle (HR=0.645, P=0.004) and High School (HR=0.472, P < 0.001) education were related ~~to significant reductions in~~to reduced CI risk. The decreased risk of CI associated with Middle education weakened with older baseline age (HR=1.029, P=0.056) and was stronger in women than men (HR=1.309, P=0.001). The association between High School and lowered CI risk, however, was not moderated by sex or baseline age, but was stronger in Asians than Whites (*HR*=1.047, P=0.044), and significant among Asian (HR=0.34, P < 0.001) and Black (HR=0.382, P=0.016), but not White, *APOE*4* carriers.

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Conclusion

~~Results imply that~~ High School completion may reduce risk of CI associated with advancing age and *APOE*4*. The observed ethnoregional differences in this effect are potentially due to variations in social, economic, and political outcomes associated with educational attainment, in combination with neurobiological and genetic differences, and warrant further study.

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The attainment of higher levels of education is related to decreased dementia incidence (Caamano-Isorna et al., 2006; Meng and D'Arcy, 2012; Sharp and Gatz, 2011; Valenzuela and Sachdev, 2006; Xu et al., 2016), and attenuated cognitive decline (Albert et al., 1995; Alley et al., 2007; Anstey and Christensen, 2000a; Anstey and Christensen, 2000b; Anstey et al., 2003; Bosma et al., 2003; Christensen et al., 1997; Colsher and Wallace, 1991; Hall et al., 2007; Leibovici et al., 1996; Zahodne et al., 2015). It has been theorised that this is in part due to education building *cognitive reserve* (CR) or brain reserve capacity~~,~~. Cognitive reserve may be characterised as more efficient brain networks and greater neural capacity, making the brain less prone to disruption. It may also reflect better compensatory neural processes in the face of neural damage, including the use of alternative brain structures and neural pathways which are normally unused by those with intact brains (Meng and D'Arcy, 2012; Stern et al., 1999). The cognitive reserve hypothesis is supported by studies finding higher levels of brain pathology and degraded functioning among AD sufferers with high versus low educational attainment, despite having comparable levels of cognitive impairment (Fratiglioni and Wang, 2007). ~~allowing~~ Because of this cognitive reserve, individuals are better able to tolerate age-related neuropathology without the expression of marked cognitive impairment(Meng and D'Arcy, 2012; Stern et al., 1999). As the degree of neuropathology advances over time, however, it may be so severe that the brain can no longer compensate for the underlying physical damage, thus leading to accelerated cognitive decline (Stern et al., 1999). This would imply that higher education may not be related to attenuated decline at very old ages (Van Dijk et al., 2008). This hypothesis has been supported by some(Butler et al., 1996; Schmand et al., 1997), but not all studies (Farmer et al., 1995; Van Dijk et al., 2008), highlighting the need for clarification.

Recent studies also indicate that the relationship between education and attenuated cognitive decline is *curvilinear*, meaning that after a certain level of educational attainment, additional

education does not contribute to further significant reductions in cognitive decline(Wilson et al., 2009). Two U.S. based studies have suggested that this may occur after completion of 8-9 years (Lyketsos et al., 1999; Zahodne et al., 2015) of formal education (i.e., *middle school*). Whether this inference can be generalised to different cohorts and settings remains to be determined.

Compared to men, women with lower education are more likely to develop dementia (Launer et al., 1999; Ott et al., 1999; Russ et al., 2013; Sharp and Gatz, 2011); however, it is currently unclear if they also decline faster. Ethnoregional differences in the relationship between education and cognitive decline are also unclear, particularly differences to Asian groups, as prior studies have mainly compared White and Black Americans (Fitzpatrick et al., 2004; Lopez et al., 2017; Sachs-Ericsson and Blazer, 2005). Finally, there are mixed results surrounding whether education can offset faster cognitive decline associated with carriage of the Apolipoprotein E epsilon 4 (*APOE*4*) allele (Duara et al., 1996; Seeman et al., 2005; Shadlen et al., 2005; Vermeiren et al., 2013; Winnock et al., 2002). Studies incorporating larger, and more diverse study samples may help to clarify these important issues.

Therefore, we aimed to pool harmonised data from 18 independent research studies participating in COSMIC (Cohort Studies of Memory in an International Consortium) to clarify the nature of the relationship between education and cognitive decline in an ethnically diverse group of older adults, and to determine how this relationship is moderated by age, sex, ethnicity, and *APOE*4* carriage.

Methods

Study Selection

We collected datasets for this meta-analysis from independent research studies participating in COSMIC; a consortium which combines data from longitudinal, population-based cohort

studies of older adults to identify factors that moderate the risk of cognitive decline(Sachdev et al., 2013). Studies were included if they collected the following Individual Participant Data (IPD) at baseline: age, sex, education (in years), data for four dementia risk factors to be treated as covariates (i.e., hypertension, diabetes, history of cardiovascular disease, history of stroke), score for a test of general mental status or cognition (typically the Mini Mental State Examination [MMSE]), self-reported ethnicity, and dementia status (details of participating studies are provided in eTable ~~1~~1). For studies lacking IPD for ethnicity, participants' ethnicity was assigned as the majority ethnicity of the study sample (as informed by each study's lead investigators). Criteria used to diagnose dementia as well as risk factor data available in each study, and how this was harmonised across studies is provided in eTable ~~3~~2. Participants that did not have the requisite data specified above, or who had dementia at baseline were excluded from all analyses. 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 meta-analysis had prior ethics approval (see eTable ~~2~~ 3 in the Supplement).

Outcome Measure

The MMSE(Folstein et al., 1975) was the primary outcome measure in this study, which was administered in all but three studies. In these three studies an alternative test of general mental status was administered, and scores converted to MMSE scores using published algorithms or co-calibration tables (see eTable ~~2~~2). MMSE scores were then converted to a binary indicator, where scores ≤ 23 indicated the presence of cognitive impairment (Tombaugh and McIntyre, 1992a; Tombaugh and McIntyre, 1992b). This cut-off has shown good sensitivity and specificity for the classification of dementia (Kochhann et al., 2010).

Synthesis Methods

A one-step IPD meta-analysis was conducted using multilevel parametric survival analysis to examine the relationship between education and risk of cognitive impairment (CI). The multilevel model included two levels (i.e., participants nested in studies). Multivariate survival analysis with ordered failure events was used to account for participants who were cognitively impaired at multiple study waves (Andersen and Gill, 1982; Twisk, 2013). For all participants, *event time* was the time (in years) at which cognitive impairment, or when censoring occurred. A *start time* variable coded the time when participants began being at risk of cognitive impairment. For censored observations, start time was 0 (i.e., time of entry into the study). For participants who experienced CI, on their subsequent dataset row, start time was the time point when they were last cognitively impaired (i.e., their most recent "failure").

Models were fit using the mestreg package in Stata 15 (StataCorp., 2013). Model terms included education in years (centred at the mean of 8.9 years), education^2, baseline age (centred at the median age of 70 years), and the interaction between both education and education^2 with baseline age (i.e., *education* x *age; education*^{2} x *age*). Covariates were sex, hypertension, diabetes, history of cardiovascular disease, history of stroke and MMSE score at baseline. To examine whether associations with education differed between sexes, two additional interactions were included: *education x sex*, and *education*^{2} *x sex*. Robust standard errors were calculated which adjusted for multiple CI events in individuals. Based on tests of model fit using likelihood ratio tests, random effects for the intercept and slope (i.e., for education), and their covariance, were included in the analysis, and a Weibull distribution was selected.

The above analyses were repeated treating education as categorical. We categorised participants into the following levels of educational attainment: (i) Incomplete Elementary; (ii) Elementary; (iii) Middle Level/Incomplete High School; and (iv) High School. The

Elementary category was treated as the reference group. If a study collected categorical educational data, participants were assigned to one of the above-mentioned categories using this data. In studies, with minimal or no available categorical data, we used the continuous years of education data to assign participants to an educational achievement level based on cut-offs specific to the country where the study was conducted (see eTable 4), which were obtained from the Scholaro website (https://www.scholaro.com).

To explore ethnic differences, we included a categorical variable in the analysis that coded ethnicity (0 = White, 1 = East/Southeast Asian, 2 = Black), and all interactions (i.e., 2-way, and 3-way) with education category and baseline age. Whites were treated as the reference. To examine whether *APOE*4* carriage moderated the association between education and cognitive impairment, we repeated the analyses above, and included a binary indicator for *APOE*4* (1 = carrier, 0 = non-carrier) and all interactions with education category and baseline age. To test for ethnic differences in the interaction between *APOE*4* and education, we included all interactions between ethnicity, *APOE*4*, and education category.

To minimise bias associated with non-random attrition, we incorporated inverse probability weighting (IPW) into all analyses(Buchanan et al., 2014). To calculate IPWs, logistic regression was used to regress a binary indicator of missingness (1 = not missing; 0 = missing) for each outcome at each wave on participants' sex, age at last measurement, years of education (and all interactions between age, sex, and education), presence of hypertension, diabetes, heart disease, and stroke, and their MMSE score, age, and time in study from their most recently completed data collection point. Predicted probabilities from each model were converted to stabilised IPWs and used as a scale weight in the analysis (Singer and Willet, 2003; Tabachnick, 2007; Thoemmes and Ong, 2015).

Results

Participant characteristics

Baseline demographic characteristics are shown Table 1. The average follow-up duration ranged between 2 and 10 years, and the mean age at baseline ranged between 63 and 81 years. The proportion of participants lost to follow-up ranged between 1% (Tajiri) and 99.9% (EAS). The rate of attrition was positively associated with the length of follow up (R = 0.9, P < 0.001). In all but two studies (PATH, MoVIES), females outnumbered males. Mean years of education ranged between 2.8 and 13.9 years across studies, with an overall mean of 9 years. For 10 studies, the majority educational attainment level was at least Middle school, whereas for the remaining 8 studies, most participants had either a complete or incomplete Elementary education. The proportion of participants who were *APOE*4* carriers ranged between 13.3 and 25.2%. IPD for ethnicity was available in six studies (Bambui, EAS, MoVIES, PATH, SydneyMAS, CHAS). In ten studies, the majority of the sample (i.e., > 60%) was White. Six studies included Asian participants. In three of these studies, the entire sample comprised of Asians. Five studies had Black participants, with the proportion ranging between 0.2 to 27.1% of the study sample. The proportion of participants that experienced cognitive impairment ranged from 2% (PATH) to 62% (Bambui).

Association between education and cognitive impairment

Results are displayed in Table 2. Overall, more years of education was related to decreased CI risk (HR=0.881, P < 0.001). The quadratic term for education ($education^2$), was small, but significant (HR=1.003, P=0.031), implying that the association between education and decreased CI risk was less pronounced at higher levels of education. Both the linear (HR=1.006, P < 0.001) and quadratic terms (HR=0.999, P=0.002) for education significantly weakened with older baseline age but were not moderated by sex.

We further explored this nonlinearity by examining education categorically. With Elementary education as the reference, the risk of CI was significantly higher for incomplete Elementary (HR=1.645, $P < 0.001$), and lower for both Middle (HR=0.645, $P=0.004$) and High School education (HR=0.472, $P < 0.001$; See Figure 1A). Additional comparisons showed that CI risk was lower for High School versus Middle education (HR=0.73, $P=0.002$). Furthermore, we separated the High School category into those that did and did not complete College Education and found no difference in CI risk between these groups (HR=0.762, $P=0.234$).

Differences in CI risk between both Incomplete Elementary (HR=0.955, $P < 0.001$; Figure 1B) and Middle education (HR =1.038, $P < 0.001$; Figure 1C) compared to Elementary education significantly weakened with older baseline age, but not so for High School education (HR=1.029, $P=0.056$). Simple effect comparisons showed that among 60 but not 80-year olds, the risk of CI was higher for incomplete Elementary (HR=2.601, $P < 0.001$), and lower for Middle versus Elementary education (HR=0.444, $P=0.003$). High School education, however, was related to decreased CI risk in both 60 (HR=0.353, $P < 0.003$) and 80-year olds (HR=0.631, $P < 0.001$).

Examining sex differences, the reduction in CI risk associated with Middle versus Elementary education was significant for women (HR=0.58, $P < 0.001$) but not men (HR=0.76, $P=0.128$), and this sex difference was significant (HR=1.309, $P=0.001$) as shown in Figure 1C. There were no sex differences in CI risk for either the Incomplete Elementary or High School categories (versus Elementary education).

As shown in Table 3, in both Asians and Whites, incomplete Elementary education was related to a significant increase in CI risk, whereas Middle and High School education were both related to a significant decrease in CI risk, relative to Elementary education. The reduction in CI risk associated with High School education, however, was significantly larger

in Asians than Whites (HR=0.575, *P*=0.002), as can be seen in Figure 2A. In addition, the reduction in CI risk associated with High School completion weakened with older baseline age to a stronger degree in Asians than Whites (*HR*=1.047, *P*=0.044).

Although differences between Whites and Blacks were not significant for each of the comparisons, Table 3 shows that neither Middle (versus Elementary), nor Elementary (versus incomplete Elementary) education were related to significant reductions in CI risk among Blacks. High School versus Elementary education, however, was related to significant reduction CI risk among Blacks (HR=0.459, *P*=0.001), as shown in Figure 2B.

As shown in Table 2, *APOE*4* carriage did not moderate differences in CI risk between education levels (treating Elementary education as the reference), and these associations were not moderated by baseline age or sex. Results in Table 2 nonetheless show that Elementary (versus incomplete Elementary) and Middle (versus Elementary) education were related to significant reductions in CI risk in non-carriers only. High School completion, however, was associated with a lowered risk of CI compared to Elementary education in both *APOE*4* carriers (HR=0.52, *P*=0.007) and non-carriers (HR=0.519, *P*=0.009).

As shown in Table 3, *APOE*4* carriage moderated the associations between Incomplete Elementary (HR=0.555, *P*=0.018) and Middle education (HR=0.304, $P < 0.001$) with CI risk differently in Whites and Asians. In Whites, Incomplete versus Complete Elementary education was associated with increased CI risk in both *APOE*4* carriers (HR=2.395, *P*=0.004) and non-carriers (HR=1.834, *P*=0.001). In Asians, however, this difference was significant for non-carriers only (HR=1.572, *P*=0.003). As shown in Figure 3A, however, Middle level (versus Elementary) education was significantly related to decreased CI risk in both Asian *APOE*4* carriers (HR=0.34, $P < 0.001$) and non-carriers (HR=0.493, $P < 0.001$); whereas in Whites, as shown in Figure 3B, this reduction in CI risk only emerged for non-

carriers (HR=0.382, *P*<0.001). Similar results emerged for the comparison between High School and Elementary education ~~as shown in Figure 3B~~, although the difference between Whites and Asians was not significant.

The interaction between *APOE*4* and education on CI risk did not significantly differ between Whites and Blacks, at any educational level. Nonetheless, results in Table 3 indicate that Elementary and Middle education were unrelated to decreased CI risk in both Black *APOE*4* carriers and non-carriers. ~~In contrast to Whites, however,~~ High School education was related to decreased CI risk in Black *APOE*4* carriers (HR=0.382, *P*=0.016), but not non-carriers, as can be seen in Figure 3C. In Whites (Figure 3D), the opposite was found, with High School education being associated with a significant decrease in CI risk in non-carriers (HR=0.448, *P*=0.002), but not in *APOE*4* carriers.

discussion

In this IPD meta-analysis, years of education was associated with a significant reduction in the risk of cognitive impairment (CI). This association, however, was non-linear, indicating that with even more years of education, the reduction in CI risk was less pronounced. Categorical analyses clarified these findings, indicating that increasing levels of educational attainment (i.e., Elementary versus Incomplete Elementary, Middle versus Elementary, and High School versus Middle) were each significantly related to decreases in CI risk. Additional analyses revealed, however, that completion of College did not decrease CI risk relative to the completion of High School. Expanding upon previous systematic reviews (Caamano-Isorna et al., 2006; Meng and D'Arcy, 2012; Sharp and Gatz, 2011; Valenzuela and Sachdev, 2006; Xu et al., 2016), our results imply that the association between education and reduction in cognitive impairment risk is not monotonically linear, in line with recent studies conducted in individual cohorts (Lyketsos et al., 1999; Wilson et al., 2009; Zahodne et al., 2015).

Our results align with those of ~~Zahodne et al.~~ Zahodne et al. (2015), who found that years of education both before (i.e., early education) and after middle school (i.e., late education) was related to attenuated cognitive decline. Importantly, they found that the association between education and cognitive decline after middle school was mediated entirely by income. They proposed that early education promotes the development of critical skills, as well as cognitive and neural development in a sensitive period of childhood, which directly contribute to latelife protection against cognitive decline. In contrast, late education influences cognitive reserve indirectly by shaping employment opportunities and income, which contribute to latelife protection against cognitive decline by increasing access to quality health care and leisure opportunities, and reducing exposure to life stressors (Zahodne et al., 2015). For the historical periods relevant to our cohorts, differences in occupational and economic outcomes between High School and college graduates were relatively small (Baum, 2014; Taylor et al., 2014). This may therefore explain why the risk of cognitive impairment was comparable between those with a High School versus College education in our study.

The reduced risk of cognitive impairment associated with Elementary (vs. Incomplete Elementary education) and Middle (vs. Elementary) education weakened with older baseline age. Namely, both associations were significant in those aged 60, but not among those aged 80 years at baseline. ~~Schmand et al.~~Schmand et al. (1997) found that high versus low education was associated with significant reduction in the magnitude of cognitive decline among participants in the youngest (i.e., 65-70 years), but not in the oldest (i.e., 80+ years) age group. Similarly, Butler et al. found that holding a bachelor's degree was associated with a larger reduction in the amount of MMSE decline in nuns aged 75-84, compared to those aged 85+ at baseline(Butler et al., 1996). Interestingly, however, we found that High School (versus Elementary) education was associated with attenuated risk of cognitive impairment in both 60 *and* 80-year-old participants, which is broadly in line with the cognitive reserve

hypothesis (Meng and D'Arcy, 2012; Stern et al., 1999; Stern et al., 1992). Namely, in 80-year-olds, the level of neurodegeneration may have been so severe that lower levels of educational attainment (i.e., Elementary, and Middle) were insufficient to compensate for age-related cognitive deficits. However, having a High School education may have provided 80-year-olds with sufficient reserve to compensate for their higher degree of neurodegeneration, thus contributing to significant reductions in cognitive impairment risk relative to those with only Elementary education.

Some studies have found no moderating effect of baseline age on the relationship between education and cognitive decline. These studies, however, have used either very low cut-offs to define the younger and older-aged groups (i.e., 65 years) (Farmer et al., 1995), examined education solely as a continuous variable (Farmer et al., 1995; Van Dijk et al., 2008), or limited their analyses to linear associations(Van Dijk et al., 2008). On the other hand, not examining age as a moderator may explain why non-significant associations between education and cognitive decline were found in previous studies (Christensen et al., 2001; Seeman et al., 2005; Van Dijk et al., 2008; Winnock et al., 2002).

Overall, we found that the protective association between Middle education and cognitive impairment was significant in women but not men. Two previous studies examining sex differences found that low education was related to increased dementia risk in women but not men (Launer et al., 1999; Ott et al., 1999). Relatedly, an IPD meta-analysis found that leaving full-time education before versus after the age of 15 was associated with an increased risk of dementia death in women and not men (Russ et al., 2013). These sex differences have been attributed to larger socioeconomic discrepancies between those with low versus high education among women than men (Ott et al., 1999). Namely, women with low education are more likely to have worse occupational attainment, lower income, poorer health, fewer leisure opportunities, and consequently poorer cognitive outcomes than low educated men (Ott et al.,

1999; Sharp and Gatz, 2011). This is evident in Figure 1D, which indicated that the sex difference was primarily attributable to larger cognitive impairment among the Elementary (low) educated women than men.

Regarding ethnoregional differences, there was a larger difference in CI risk between the Elementary and High School education categories in Asians than Whites. Historically, in some Asian countries (e.g. Japan), those that received a High School education likely had better socioeconomic status than those who did not (Sorensen, 1994). In addition, educational systems in Hong Kong and South Korea were in disarray around the time of the Second World War (WWII), and illiteracy rates were high ~~;~~ (Sorensen, 1994) implying that the quality of early education was poor in Asian countries during this period. Collectively, this suggests that the discrepancy between Elementary and High School education reflects wider gaps in educational quality and socioeconomic outcomes among Asians than Whites, hence leading to larger differences in cognitive performance between those with an Elementary versus High School education in Asians compared to Whites.

In contrast to Whites, in Blacks there was no significant reduction in CI risk associated with an Elementary (versus Incomplete Elementary) or Middle (versus Elementary) education, implying that early education was not protective in this group. This is possibly reflective of historical gaps in access to quality education between Blacks and Whites (Boozer et al., 1992; Carvalho et al., 2015), such that critical skills (e.g., reading, writing) were not adequately instilled among Blacks. Indeed, studies have found that differences in cognitive outcomes between Whites and Blacks are reduced after controlling for illiteracy (Carvalho et al., 2015; Sachs-Ericsson and Blazer, 2005). Interestingly, however, High School completion was associated with a significant reduction in CI risk among Blacks, and the size of this effect comparable to Whites. This aligns with ~~Shadlen et al.~~ Shadlen et al. (2006), who found that dementia incidence was significantly lower for Black Americans who had more (versus less)

than 10 years of education. ~~Fitzpatrick et al.~~Fitzpatrick et al. (2004), however, found no significant differences in dementia incidence for Blacks with and without a High School education, although they didn't control for vascular risk factors or baseline cognition. Our results suggest that only late education reduced CI risk among Blacks. ~~Hall and colleagues~~Hall et al. (2000) argued that, historically, for a Black American to attain an education beyond Middle school, they likely would have overcome economic deprivation, poverty, rural life, and acquired psychological resilience, collectively building their cognitive reserve, and thereby reducing their risk of cognitive impairment. We emphasise, however, that without access to relevant data, these proposed mechanisms are speculative at best.

Finally, we found no significant differences in the relationship between educational attainment and CI between *APOE*4* carriers and non-carriers. Results showed, however, that only High School attainment was related to reduced CI risk in *APOE*4* carriers, implying that a higher degree of cognitive reserve is needed to counteract faster cognitive decline associated with *APOE*4*. Similarly, Shadlen et al. (2005) ~~Shadlen et al.(Seeman et al., 2005)~~ found that there were greater reductions in the magnitude of cognitive decline in *APOE*4* homozygotes with increasing years of education. Our ethnoregional analyses, however, indicated that High School completion was related to a reduced risk of cognitive impairment (relative to Elementary school) in Asian and Black, but not White, *APOE*4* carriers. Furthermore, Middle education was related to decreased CI risk in Asian *APOE*4* carriers. As discussed above, differences between lower and higher levels of education, in particular completing versus not completing High School, may reflect wider gaps in socioeconomic status (Hall et al., 2000; Sharp and Gatz, 2011), literacy (Sachs-Ericsson and Blazer, 2005), occupational complexity (Andel et al., 2006), income (Zahodne et al., 2015), and health outcomes (Williams et al., 2016) in Asians and Blacks than in Whites. Each of these factors is associated with reduced dementia incidence (Andel et al., 2006; Russ et al., 2013; Sharp and

Gatz, 2011). This implies that higher educational attainment is correlated with larger reductions in *multiple* dementia risk factors in Blacks and Asians compared to Whites. Consequently, this may explain why High School attainment was associated with significant attenuation of CI risk in Asian and Black, but not White *APOE*4* carriers. Interestingly, Elementary versus Incomplete Elementary education was related to reduced CI risk in White *APOE*4* carriers only. We speculate that poor-quality Elementary Education available to Asians and Blacks in previous decades may not have built a sufficient level of cognitive reserve to overcome *APOE*4*-mediated cognitive impairments in these ethnic groups.

Because of limited access to relevant data, it is not possible for us to disentangle whether the reductions in cognitive impairment are primarily due to cognitive reserve or other variables that education is a proxy for (e.g., income, socioeconomic status, access to healthcare). This also precludes our ability to investigate more complex research questions, including the factors that mediate reductions in CI risk associated with education. We were also not able to control for literacy levels, which may (in part) account for the observed ethnic, gender, and age (and/or cohort) differences in the relationship between education and cognitive impairment. Our study is, however, strengthened by our large and diverse sample; our ability to control for several possible confounders/vascular risk factors; use of inverse probability weighting to reduce bias in parameter estimates due to non-random attrition; and the availability of educational IPD, enabling us to classify participants into finer-grained, educational categories. The cut-offs used to classify participants into these levels of achievement, furthermore, were tailored to the specific educational system of that country, thus enhancing the generalisability of our findings.

In this IPD meta-analysis of 18 population-based studies, we found that compared to Elementary education, attainment of a Middle or High School education was related to significant reduction in the risk of cognitive impairment. There was, however, no difference

in CI risk between those with a complete High School or Tertiary education. The decreased CI risk associated with Middle education weakened with older baseline age and was stronger in women than men. The reduced risk of CI associated with High School completion, however, was unrelated to sex or baseline age, but emerged stronger in Asians than Whites. Finally, High School completion was related to reduced CI risk in *APOE*4* carriers, specifically among those of Asian and Black ethnicity. High School completion may potentially reduce the risk of CI associated with advancing age and carriage of *APOE*4* among non-White ethnic groups. The emergent ethnic differences may be attributable to historically wider gaps in socioeconomic status, employment opportunities, income, and health between low and high educated individuals in Asian and Black, versus White populations. Limited access to this data precludes us from making definitive conclusions about ethnic differences in how education influences the trajectory of cognitive decline in late adulthood. This limitation points to the challenges of studying ethnic differences in cognitive ageing, particularly in relation to examining differential impacts of risk and protective factors between and within ethnic groups (Brewster et al., 2019). A complete and unbiased analysis of risk factors take into account ethnoregional differences in genetics (e.g., ethnicity-specific genetic risk factors for Alzheimer's Disease), biology, early life deprivation, neighbourhood characteristics (e.g., economically disadvantaged, ethnically homogenous), social and political history (e.g., experiences of discrimination and policies promoting inequality), health outcomes (e.g., vulnerability to cerebrovascular risk factors), income and employment across the lifespan, attitudes to the care of older adults with dementia (e.g., nursing home versus family care) and a wide range of other factors (Glymour and Manly, 2008). Historically, however, studies of normative ageing have been limited to non-Latino white participants, and therefore access to this rich data has been limited. Furthermore, cognitive tests used to inform

dementia diagnoses are sensitive to educational attainment adding further complexity to unbiased assessment of cognitive decline across ethnic groups (Glymour and Manly, 2008).

Besides data and measurement limitations, the consideration of complex social, political, and biological factors and how they interact with risk and protective factors (e.g., education) of cognitive ageing calls for the greater use of *complex systems models*, where interrelations and interactions among multiple levels of relevant variables can be modelled (Brewster et al., 2019). Here the impact of risk factors on cognitive outcomes can be examined in the context of a complex interplay of biological, clinical, political, and social factors. Such models have been used to examine determinants of racial and ethnic disparities in obesity and HIV transmission, and their application to cognitive ageing provides a promising avenue for future research. ~~(59)~~

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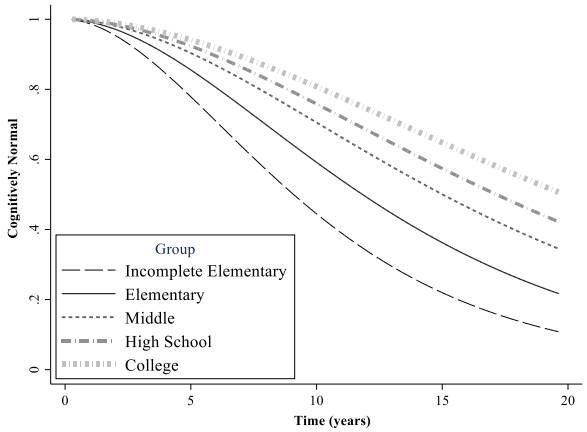
FIGURE LEGENDS

A)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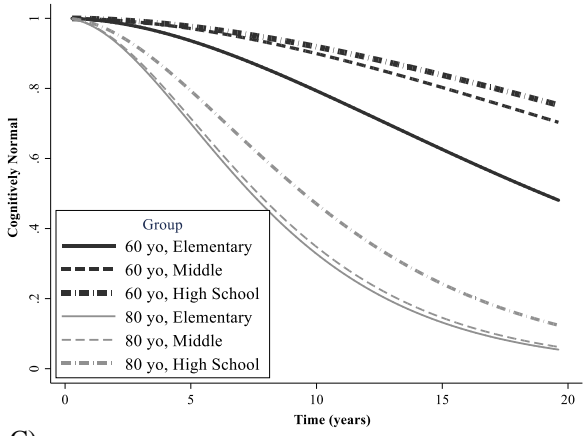
1
0
5
10
15
20
Time (years)
Group
Incomplete Elementary
Elementary
Middle
High School
College

B)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0
5
10
15
20
Time (years)
Group
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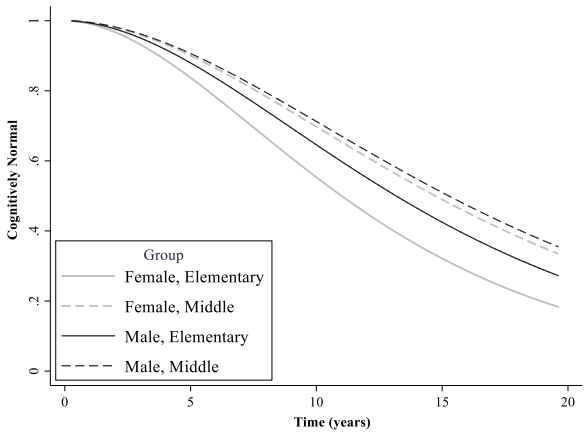
60 yo, Middle
60 yo, High School
80 yo, Elementary
80 yo, Middle
80 yo, High School

C)


Cognitively Normal
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0
5
10
15
20
Time (years)
Group
Female, Elementary
Female, Middle
Male, Elementary
Male, Middle

Figure 1. Relationship between education and risk of cognitive impairment (i.e., MMSE ≤ 23).A) Proportion of participants cognitively unimpaired over time for participants in each of the educational attainment categories. B) Proportion of cognitively unimpaired participants aged 60 and 80 years at baseline with either an Incomplete Elementary, Elementary, or High School education. C) Proportion of cognitively unimpaired men and women at baseline with either an Elementary or Middle education.

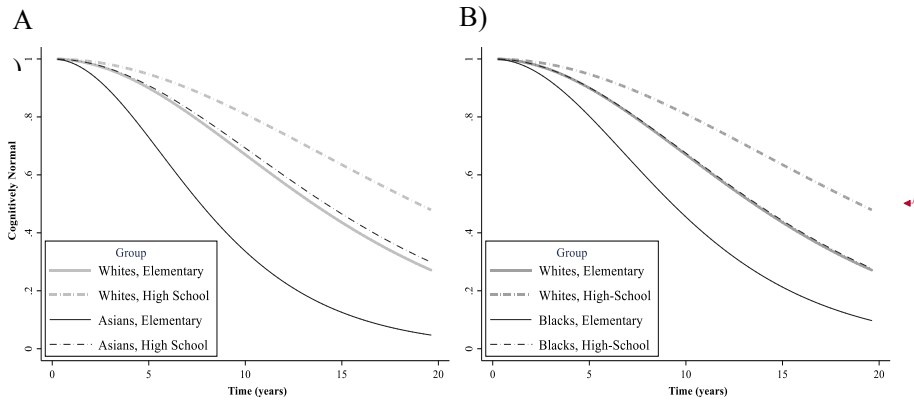

Figure 2. Ethnoregional differences in risk of cognitive impairment between education groups. A) Proportion of cognitively unimpaired White and Asian participants with an Elementary or High School education. B) Proportion of cognitively unimpaired White and Black participants with an Elementary or High School education

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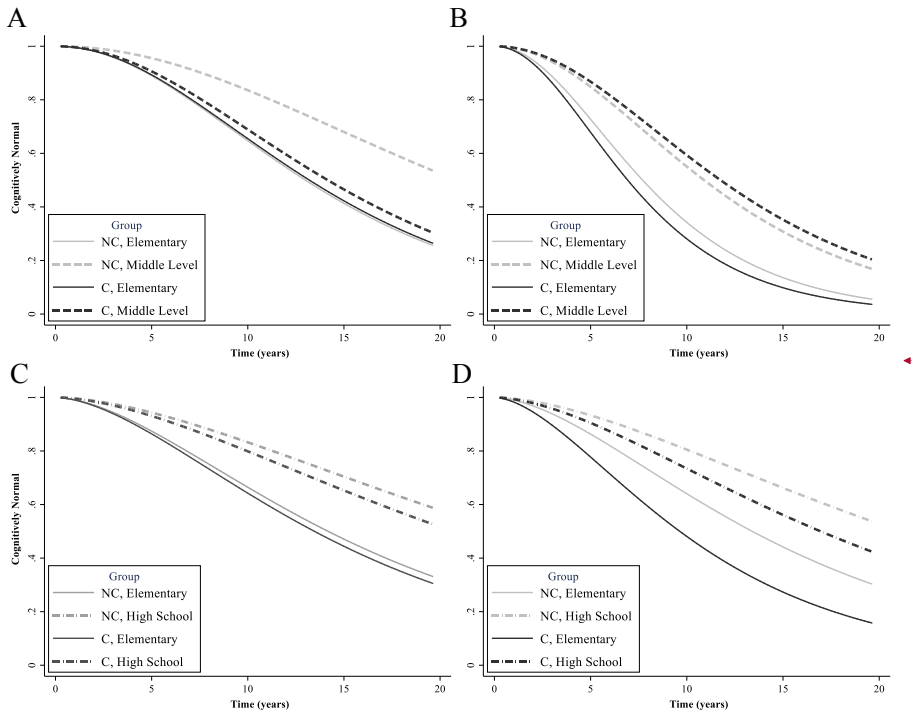

Figure 3. Interaction between educational level and carriage of *APOE*4* on the risk of cognitive impairment in ethnoregional groups. A) Proportion of cognitively unimpaired Asian *APOE*4* carriers and non-carriers with an Elementary or Middle education. B) Proportion of cognitively unimpaired White *APOE*4* carriers and non-carriers with an Elementary or Middle education. C) Proportion of cognitively unimpaired Black *APOE*4* carriers and non-carriers with an Elementary or High School education. D) Proportion of cognitively unimpaired White *APOE*4* carriers and non-carriers with an Elementary or High School education. Abbreviations: C, *APOE*4* carriers; NC, *APOE*4* non-carriers.

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Figure 3. Interaction between educational level and carriage of *APOE*4* on the risk of cognitive impairment in ethnoregional groups. A) Proportion of cognitively unimpaired White *APOE*4* carriers and non-carriers with an Elementary or Middle education. B) Proportion of cognitively unimpaired Asian *APOE*4* carriers and non-carriers with an Elementary or Middle education. C, Proportion of cognitively unimpaired White *APOE*4* carriers and non-carriers with an Elementary or High School education. D, Proportion of cognitively unimpaired Black *APOE*4* carriers and non-carriers with an Elementary or High School education. Abbreviations: C, *APOE*4* carriers; NC, *APOE*4* non-carriers.

Table 1. *Descriptive Statistics of Each Included Study at Baseline*

				Sex			Education					Covariates					Ethnicity				
	N	Lost to follow up	Impaired	Female	Age, y	Follow up, y	Education, y	Incomplete Elementary	Elementary	Middle Level	High School	CVD	DIAB	HT	Stroke	*APOE *4* carrier	White	Asian	Black	Other	Missing
Study	Analysed[a]	(%)	N (%)	%	M (SD)	M (SD)	M (SD)	%[b]	%	%	%	%	%	%	%	%	%	%	%	%	%
BAMBUI[c]	1329	72.4	827 (62.2)	62.4	68.6 (6.9)	10.1 (4.7)	2.9 (3)	88.1	5.3	4.2	2	15.5	14.8	68.2	3.5	25.2	60.7		2.3	36.9	
CAS	1464	0	222 (15.2)	66.0	73.7 (6.4)	4.6 (0.9)	9.5 (4.7)	21.8	32.2	-	46	29.5	31.8	75.7	6.0	16.7	67.9		16.3	10.4	5.4
CFAS	8253	63.2	1951 (23.6)	58.6	74.3 (6.4)	4.9 (3.8)	10.1 (2.3)	0.7	5.4	65.5	28.5	17.3	5.5	32.5	5.9	24.0	64.7		0.2	0.1	35.0
EAS	1220	99.8	220 (18)	61.6	78.1 (5.4)	4.4 (3.3)	13.6 (3.5)	0.4	3.5	16.6	79.5	33.7	16.2	63.9	9.0	22.2	68.5	0.4	27.1	3.9	
ESPRIT[d]	1916	36.3	220 (11.5)	59.3	72.9 (5.4)	6 (2.3)	10.4 (3.7)	23.4	18.2	10.7	47.7	19.5	8.8	71.4	3.2	19.3	100.0				
HELIAD[d]	419	0	69 (16.5)	59.2	71.9 (5.8)	2.8 (0.6)	6.3 (3.2)	23.4	60.9	3.1	12.6	21.0	15.8	64.9	6.9	17.2	100.0				
HK-MAPS[d]	561	24.4	169 (30.1)	54.4	72 (7)	4.6 (1.5)	5 (4.7)	55.4	19.6	10	15	16.4	18.2	49.9	7.3	13.3		100.0			
Invece.Ab[d]	977	0	32 (3.3)	52.6	72.1 (1.3)	2.2 (0.2)	7.1 (3.3)	7.2	51.1	31.7	10	27.3	18.0	60.6	7.6	18.4	100.0				
KLOSCAD[d]	4331	0	787 (18.2)	56.3	69.3 (6.2)	2 (0.3)	8.7 (5.3)	21.4	25.9	13.3	39.4	13.2	26.9	61.2	9.4	25.4		100.0			
LEILA[d]	766	93.6	208 (27.2)	73.4	81.1 (4.6)	5.4 (3.3)	12 (1.8)			21.5	78.3	8.1	22.8	81.7	6.5	16.0	100.0				
MoVIES	368	83.2	201 (54.6)	49.2	74.6 (6.1)	7.9 (4.1)	10.6 (2.7)	1.4	33.7	16	48.9	41.3	14.1	70.4	9.2	25.1	96.7		3.3		
PATH	2212	13.5	44 (2)	48.4	62.5 (1.5)	7.5 (1.4)	13.9 (2.7)	0.8	10.1	35.4	53.8	14.8	7.1	65.7	3.9	27.1	96.1	2.4		0.0	1.5
SALSA[d]	1438	47.1	359 (25)	58.3	70.1 (6.6)	6.3 (2.4)	7.6 (5.4)	33.4	17	17.5	32.1	22.2	31.4	67.5	8.2	14.2				100.0	
SGS[d]	842	0	47 (5.6)	57.2	72.8 (5.6)	2 (0)	11.4 (2.6)	0.5	8.1	36.5	55	12.4	12.7	37.2	3.3	b		100.0			
SLASI[d]	432	44.2	41 (9.5)	62.5	64.7 (6.7)	2.9 (1.2)	7 (4.4)	32.1	21	9.6	37.3	10.0	12.8	60.7	3.0	16.6		100.0			
SydneyMAS	891	25.5	76 (8.5)	54.3	78.5 (4.7)	5.2 (1.4)	11.7 (3.5)	2.1	42.6	20.1	35.1	28.5	15.3	82.9	3.9	22.7	98.0	1.0			1.0
ZARADEMP	3161	25.3	521 (16.5)	55.5	71.9 (8.7)	4.1 (1.2)	7.6 (3.9)	41.5	40.2	3.7	14.6	6.7	12.3	67.8	4.8	b	100.0				
Tajiri[c]	98	0	18 (18.4)	57.1	71.1 (3.9)	5 (0)	8.1 (1.8)	5.1	76.5	13.3	5.1	2.0	10.2	71.4	0	b		100.0			

Abbreviations: APOE*4, Apolipoprotein E ε4; Bambui, Bambui Cohort Study of Aging; CHAS, Cuban Health and Alzheimer Study; CVD, cardiovascular disease history; DIAB, diabetes, EAS, Einstein Aging Study; ESPRIT, Etude Santé Psychologique et Traitement; HELIAD, Hellenic Longitudinal Investigation of Aging and Diet; HK-MAPS, Hong Kong Memory and Ageing Prospective Study; HT, hypertension; Invece.Ab, Invecchiamento Cerebrale in Abbiategrasso; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; LEILA75+, Leipzig Longitudinal Study of the Aged; MoVIES, Monongahela Valley Independent Elders Survey; PATH, Personality and Total Health

Through Life Project; SALSA, Sacramento Area Latino Study on Aging; SGS, Sasaguri Genkimon Study; SLASI, Singapore Longitudinal Ageing Studies; SydneyMAS, Sydney Memory and Ageing Study; ZARADEMP, Zaragoza Dementia Depression Project.

[a] Refers to the number of participants used in survival analysis. This includes participants with data for age at baseline, sex, education, all covariates, and have valid time-to-event information. Participants that dropped out at the initial wave are excluded from survival analyses because no time to event information is available

[b] Values in percentages are in relation to analysed sample (i.e., those with time-to-event information). Percentages may sum to less or more than 100 due to rounding error. Current smoking and high cholesterol were not used as covariates in the analysis as data for these variables was not available in all studies (Bambui did not have data on individuals who were non-smokers, and the KLOSCAD, LEILA, and MoVIES studies lacked data on high cholesterol).

[c] Data relating to ethnicity in the Bambui study derived from a variable coding the skin colour of participants. For the purposes of ethnoregional analyses, however, the ethnicity of all participants in Bambui was regarded as Brazilian, as advised by the chief investigators of this study, and consequently all participants in this study were excluded from comparisons between Whites and Asians.

[d] IPD for ethnicity was not available in these studies. Participants were assigned to the majority ethnic group of the study sample based on the recommendations of each study's lead investigator(s).

Table 2. *Results of Parametric Survival Analysis Examining Association Between Education and Risk of Cognitive Impairment and Moderation by Age, Sex, and APOE*4*

	HR (95% confidence interval)	**P**
Continuous		
Education	0.881, (0.847-0.916)	0.000
Education x Age	1.006, (1.003-1.01)	0.000
Education effect at 80 y	0.94, (0.913-0.968)	0.000
Education effect at 60 y	0.826, (0.773-0.883)	0.000
Education^2	1.003, (1-1.006)	0.031
Education^2 x Age	0.999, (0.999-1)	0.002
Education^2 effect at 80 y	0.997, (0.991-1.004)	0.409
Education^2 effect at 60 y	1.009, (1.007-1.012)	0.000
Education x Sex	1.026, (0.997-1.055)	0.074
Education^2 x Sex	1.001, (0.995-1.008)	0.743
Categorical		
Incomplete Elementary	1.645 (1.324-2.045)	0.000
Incomplete Elementary x Age	0.955 (0.933-0.978)	0.000
Old	1.041 (0.771-1.406)	0.794
Young	2.601 (1.854-3.648)	0.000
Incomplete Elementary x Sex	1.002 (0.754-1.33)	0.991
Female	1.625 (1.328-1.988)	0.000
Male	1.627 (1.163-2.277)	0.005
Middle Level	0.645 (0.479-0.87)	0.004
Middle Level x Age	1.038 (1.009-1.067)	0.009
Old	0.937 (0.765-1.147)	0.527
Young	0.444 (0.259-0.763)	0.003
Middle Level x Sex	1.309 (1.109-1.545)	0.001
Female	0.58 (0.438-0.769)	0.000
Male	0.76 (0.533-1.083)	0.128
High School	0.472 (0.312-0.715)	0.000
High School x Age	1.029 (0.999-1.061)	0.056
Old	0.631 (0.489-0.815)	0.000
Young	0.353 (0.18-0.694)	0.003
High School x Sex	1.215 (0.968-1.525)	0.093
Female	0.437 (0.296-0.643)	0.000
Male	0.53 (0.326-0.862)	0.011
High School versus Middle Level	0.732 (0.599-0.894)	0.002
College versus High School (some College)	0.762 (0.487-1.192)	0.234
College v Middle	0.595 (0.345-1.026)	0.062
College v Elementary	0.381 (0.184-0.788)	0.009
Education and *APOE*4*		

Incomplete Elementary		
APOE*4 x Incomplete Elementary	0.906 (0.66-1.244)	0.543
Incomplete Elementary (NC)	1.526 (1.226-1.901)	0.000
Incomplete Elementary (C)	1.383 (0.953-2.008)	0.088
APOE*4 x Incomplete Elementary x Age	0.998 (0.956-1.04)	0.910
APOE*4 x Incomplete Elementary x Sex	0.928 (0.602-1.432)	0.737
Middle		
APOE*4 x Middle	1.505 (0.946-2.394)	0.084
Middle (NC)	0.496 (0.316-0.78)	0.002
Middle (C)	0.747 (0.454-1.229)	0.251
APOE*4 x Middle x Age	0.977 (0.929-1.027)	0.355
APOE*4 x Middle x Sex	0.961 (0.577-1.6)	0.879
High School		
APOE*4 x High School	1.002 (0.62-1.619)	0.994
High School (NC)	0.519 (0.316-0.851)	0.009
High School (C)	0.52 (0.324-0.834)	0.007
APOE*4 x High School x Age	1.014 (0.973-1.058)	0.505
APOE*4 x High School x Sex	1.458 (0.868-2.45)	0.154

Abbreviations: APOE*4, Apolipoprotein E ε4; C, APOE*4 carrier; NC, APOE*4 non-carrier;

[a] ~~Reference Group~~

[b] ~~Because of the small numbers of Black APOE*4 carriers in the low education groups, the Elementary and Incomplete Elementary groups were collapsed and treated as the reference education group.~~

Table 3. *Ethnicity Differences in the Association Between Education and Risk of Cognitive Impairment, and oderation by Age and APOE*4.*

	Asians		**Blacks**		**Whites**	
	HR (95% confidence interval)	**p**	**HR (95% confidence interval)**	**p**	**HR (95% confidence interval)**	**p**
Education						
Incomplete Elementary						
Incomplete Elementary x Ethnicity	0.87 (0.676-1.119)	0.278	0.866 (0.431-1.743)	0.688	1[a]	
Within Ethnic Group: Incomplete Elementary	1.631 (1.535-1.734)	0.000	1.625 (0.768-3.437)	0.204	1.875 (1.454-2.418)	0.000
Incomplete Elementary x Age	0.977 (0.942-1.013)	0.208	0.993 (0.908-1.087)	0.879	1[a]	
Within Ethnic Group: Incomplete Elementary x Age	0.943 (0.911-0.977)	0.001	0.959 (0.88-1.045)	0.341	0.966 (0.954-0.978)	0.000
Middle						
Middle Level x Ethnicity	0.984 (0.675-1.434)	0.934	1.664 (0.759-3.649)	0.204	1[a]	
Within Ethnic Group: Middle	0.595 (0.405-0.875)	0.008	1.006 (0.443-2.287)	0.988	0.605 (0.507-0.721)	0.000
Middle Level x Age x Ethnicity	0.972 (0.944-1.001)	0.058	1.014 (0.887-1.16)	0.837	1[a]	
Within Ethnic Group: Middle x Age	1.015 (0.996-1.035)	0.121	1.059 (0.927-1.211)	0.399	1.044 (1.018-1.072)	0.001
High School						
High School x Ethnicity	0.575 (0.406-0.815)	0.002	0.909 (0.573-1.442)	0.685	1[a]	
Within Ethnic Group: High School	0.29 (0.238-0.354)	0.000	0.459 (0.287-0.734)	0.001	0.505 (0.363-0.704)	0.000
High School x Age x Ethnicity	1.047 (1.001-1.094)	0.044	1.002 (0.925-1.085)	0.968	1[a]	
Within Ethnic Group: High School x Age	1.078 (1.038-1.12)	0.000	1.032 (0.959-1.11)	0.404	1.03 (1.008-1.052)	0.007
Education and *APOE*4*						
Incomplete Elementary						
APOE x Incomplete Elementary x Ethnicity	0.555 (0.34-0.905)	0.018	[b]		1[a]	
Within ethnicity: APOE*4 x Incomplete Elementary	0.725 (0.496-1.06)	0.097	[b]		1.306 (0.854-1.997)	0.217
Incomplete Elementary (NC)	1.572 (1.161-2.129)	0.003	[b]		1.834 (1.269-2.65)	0.001
Incomplete Elementary (C)	1.139 (0.669-1.939)	0.631	[b]		2.395 (1.325-4.329)	0.004
Middle Level						
APOE x Middle x Ethnicity	0.304 (0.182-0.507)	0.000	1.039 (0.683-1.58)	0.859	1[a]	-
Within Ethnicity: APOE*4 x Middle Level	0.69 (0.505-0.943)	0.020	2.366 (1.435-3.901)	0.001	2.271 (1.457-3.538)	0.000
Middle (NC)	0.493 (0.403-0.602)	0.000	0.634 (0.295-1.362)	0.243	0.382 (0.275-0.529)	0.000
Middle (C)	0.34 (0.257-0.449)	0.000	1.5 (0.957-2.352)	0.077	0.867 (0.545-1.379)	0.547
High School						
APOE*4 x High School x Ethnicity	0.636 (0.362-1.118)	0.116	0.731 (0.316-1.692)	0.465	1[a]	
Within Ethnicity: APOE x High School	0.896 (0.676-1.187)	0.444	0.83 (0.322-2.138)	0.700	1.408 (0.804-2.466)	0.231
High School ~~NC~~ (NC)	0.27 (0.182-0.4)	0.000	0.461 (0.16-1.324)	0.150	0.448 (0.268-0.751)	0.002
High School (C)	0.242 (0.204-0.287)	0.000	0.382 (0.175-0.834)	0.016	0.632 (0.349-1.143)	0.129

Abbreviations: APOE*4, Apolipoprotein E ε4; C, APOE*4 carrier; NC, APOE*4 non-carrier;

[a] Reference Group

[b] Because of the small numbers of Black APOE*4 carriers in the low education groups, the Elementary and Incomplete Elementary groups were collapsed and treated as the reference education group.

Supplementary Tables

eTable 1. 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 (ΒΕΥ846Ψ8Ν2-32Π)
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)
MAAS	Ethics committee of Maastricht University Medical Centre (MEC05-107)
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)
SGS	Institutional Review Board of the Institute of Health Science, Kyushu University (IHS-2010-22)
SLASI	National University of Singapore Institutional Review Board (Reference Code: 04-140)
SPAH	Ethical Committee for the Analysis of Research Projects (CAPesq) – Hospital das Clínicas and Medical School – Project Registry Number: 257/2002; National Ethical Committee on Research (CONEP-Brazil) – Project Registry Number: 4355
Sydney-MAS	University of New South Wales Human Research Ethics Committee (approval #14327)

~~Tajiri~~	~~Ethical Committee of Tohoku University Graduate School of Medicine (#2012276, #2014160, #20141238, and #20141767)~~
~~ZARADEMP~~	~~Ethics committee of the Zaragoza University Hospital (CEICA # CP16/2012)~~

~~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).~~

eTable 2. Information Relating to all Twenty Participating COSMIC Studies

Study	Abbreviation	Location	Main race/ethnicity	Sample size	Years run	Reference
Bambui Cohort Study of Aging	Bambui	Bambui, Brazil	Brazilian	1491	1997–2013	Lima-Costa et al.(Lima-Costa et al., 2011)
Cognitive Function & Ageing Study	CFAS	United Kingdom†	White	12256	1989–	Brayne et al.(Brayne et al., 2006)
Cuban Health and Alzheimer Study	CHAS	Havana and Matanzas, Cuba	White, Black, Mixed	2574	2003–	Llibre-Rodriguez et al.(Llibre-Rodriguez et al., 2017)
Einstein Aging Study	EAS	New York, USA	White, Black	2063	1993–	Katz et al.(Katz et al., 2012)
Etude Santé Psychologique et Traitement	ESPRIT	Montpellier, France	White	2187	1999–	Ritchie et al.(Ritchie et al., 2010)
Hellenic Longitudinal Investigation of Aging and Diet	HELIAD	Larissa and Marousi, Greece	White	1174	2010–	Dardiotis et al.(Dardiotis et al., 2014)
Hong Kong Memory and Ageing Prospective Study	HK-MAPS	Hong Kong	Chinese	785	2005–	Wong et al.(Sachdev et al., 2013)
Invecchiamento Cerebrale in Abbiategrasso	Invece.Ab	Abbiategrasso, Italy	White	1267	2010–2015	Guaita et al.(Guaita et al., 2013)
Korean Longitudinal Study on Cognitive Aging and Dementia	KLOSCAD	South Korea (nation-wide)	Korean	6513	2009–	Kim et al.(Han et al., 2018)
Leipzig Longitudinal Study of the Aged	LEILA75+	Leipzig, Germany	White	1040	1997–2014	Riedel-Heller et al.(Riedel-Heller et al., 2001)
Monongahela Valley Independent Elders Survey	MoVIES	Mid-Monongahela Valley, PA, USA	White	1613	1987–2002	Ganguli et al.(Ganguli et al., 2000)
Personality and Total Health Through Life Project	PATH	Canberra, Australia	White	2545	2001–	Anstey et al.(Anstey et al., 2012)

~~Sacramento Area Latino Study on Aging~~	~~SALSA~~	~~Sacramento Valley, CA, USA~~	~~Hispanic; Mexican ancestry~~	~~1710~~	~~1998–2008~~	~~Haan et al.(Haan et al., 2003)~~
~~Sasaguri Genkimon Study~~	~~SGS~~	~~Sasaguri, Japan~~	~~Japanese~~	~~793~~	~~2011–~~	~~Narazaki et al.(Narazaki et al., 2013)~~
~~Singapore Longitudinal Ageing Studies (I)~~	~~SLASI~~	~~Singapore~~	~~Chinese~~	~~1858~~	~~2003–~~	~~Feng et al.(Feng et al., 2010)~~
~~Sydney Memory and Ageing Study~~	~~Sydney MAS~~	~~Sydney, Australia~~	~~White~~	~~1037~~	~~2005–~~	~~Sachdev et al.(Sachdev et al., 2010)~~
~~Tajiri Project~~	~~Tajiri~~	~~Tajiri, Japan~~	~~Japanese~~	~~100~~	~~1998–2005~~	~~Meguro et al.(Meguro et al., 2007)~~
~~Zaragoza Dementia Depression Project~~	~~ZARADEMP~~	~~Zaragoza, Spain~~	~~White~~	~~4542~~	~~1994–~~	~~Lobo et al.(Lobo et al., 2005)~~

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Cognitive Function & Ageing Study	CFAS	United Kingdom†	White	12256	1989–	Brayne et al. (2006)
Cuban Health and Alzheimer Study	CHAS	Havana and Matanzas, Cuba	White, Black, Mixed	2574	2003–	Llibre-Rodriguez et al. (2017)
Einstein Aging Study	EAS	New York, USA	White, Black	2063	1993–	Katz et al. (2012)
Etude Santé Psychologique et Traitement	ESPRIT	Montpellier, France	White	2187	1999–	Ritchie et al. (2010)
Hellenic Longitudinal Investigation of Aging and Diet	HELIAD	Larissa and Marousi, Greece	White	1174	2010–	Dardiotis et al. (2014)
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Invecchiamento Cerebrale in Abbiategrasso	Invece.Ab	Abbiategrasso, Italy	White	1267	2010–2015	Guaita et al. (2013)
Korean Longitudinal Study on Cognitive Aging and Dementia	KLOSCAD	South Korea (nation-wide)	Korean	6513	2009–	Han et al. (2018)
Leipzig Longitudinal Study of the Aged	LEILA75+	Leipzig, Germany	White	1040	1997–2014	Riedel-Heller et al. (2001)

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Sydney Memory and Ageing Study	Sydney MAS	Sydney, Australia	White	1037	2005–	Sachdev et al. (2010)
Tajiri Project	Tajiri	Tajiri, Japan	Japanese	100	1998–2005	Meguro et al. (2007)
Zaragoza Dementia Depression Project	ZARADEMP	Zaragoza, Spain	White	4542	1994–	Lobo et al. (2005)

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eTable ~~3~~2. 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	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	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	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(Crane et al., 2008)	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(Thal et al., 1986).	1. Blood pressure (mean of 2) 2. History	Myocardial infarction, coronary artery bypass, angina, heart failure, angioplasty, or arrhythmia	1. History 2. Treatment 3. Fasting blood glucose	Medical history of stroke

Study	Criteria used to classify dementia	General Cognition test	Hypertension[a]	Cardiovascular disease[b]	Diabetes[c]	Stroke[d]
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	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 or 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	History	Coronary disease, myocardial infarction, congestive heart failure, arrhythmia, or any other heart disease	History	Medical history of stroke or TIA
HK-MAPS	Clinical Dementia Rating ≥1	MMSE	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 severity rating 1+ for cerebrovascular disease (CVA, TIA)
Invece.Ab	DSM-IV	MMSE	1. Medication 2. Supine blood pressure 170-180 mmHg and history	1. Cardiovascular disease defined by study as any of myocardial infarction, heart failure, angina, arrhythmia,	1. Treatment 2. History	History of stroke or TIA

Study	Criteria used to classify dementia	General Cognition test	Hypertension[a]	Cardiovascular disease[b]	Diabetes[c]	Stroke[d]
			3. Supine blood pressure >180 mmHg	coronary artery bypass graft, or other 2. Medication 3. Atrial fibrillation		
KLOSCAD	DSM-IV	MMSE	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 indicated 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	1.Blood pressure	Self-reported myocardial infarction	Self-reported	Self-reported history of stroke
~~MAAS~~	~~MMSE score <24~~	~~MMSE~~	~~1. Blood pressure (mean of 5)~~ ~~2. Medication~~	~~Self-reported myocardial infarction, angina, heart insufficiency, heart valve disease, bypass surgery, or open-heart surgery~~	~~Self-reported diagnosis or starting medication age 40+~~	~~**Not available.**~~
MoVIES	Clinical Dementia Rating ≥1	MMSE	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	History (includes reported presence >1 month ago at wave 2)	History of stroke (includes participants assessed at wave 2 indicating presence >1 month ago)

Study	Criteria used to classify dementia	General Cognition test	Hypertension[a]	Cardiovascular disease[b]	Diabetes[c]	Stroke[d]
				presence >1 month ago at wave 2)		
PATH	DSM-IV	MMSE	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(Crane et al., 2008)	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
SGS	Self-reported medical history	MMSE	Self-reported history of diagnosis	Self-reported history of diagnosis	Self-reported history of diagnosis	Self-reported history of diagnosis
SLASI	DSM-IV	MMSE	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
~~SPAH~~	~~DSM-IV~~	~~MMSE~~	~~1. Blood pressure (mean of 3 readings)~~ ~~2. Medication~~	~~**Not available.**~~	~~1. Fasting blood glucose~~ ~~2. Treatment~~	~~Diagnosis of stroke or TIA~~
Sydney MAS	DSM-IV	MMSE	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

Study	Criteria used to classify dementia	General Cognition test	Hypertension[a]	Cardiovascular disease[b]	Diabetes[c]	Stroke[d]
Tajiri	Clinical Dementia Rating ≥1, with DSM-IV follow-up	MMSE	1. Blood pressure (mean of 2) 2. Medication	Ischemic heart disease, or atrial fibrillation	1. Fasting blood glucose 2. Treatment (diet)	Medical history
ZARADEMP	DSM-IV	MMSE	Diagnosis using EURODEM Risk Factor Questionnaire and medical records	Diagnosis of myocardial infarction or angina using EURODEM Risk Factor Questionnaire and medical records	Diagnosis using EURODEM Risk Factor Questionnaire and medical records	History 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.

eTable 3. 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 (BEY846Ψ8N2-32Π)
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)
SGS	Institutional Review Board of the Institute of Health Science, Kyushu University (IHS-2010-22)
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)
Tajiri	Ethical Committee of Tohoku University Graduate School of Medicine (#2012276, #2014160, #20141238, and #20141767)
ZARADEMP	Ethics committee of the Zaragoza University Hospital (CEICA # CP16/2012)

Written consent was exclusively or predominantly obtained from participants in all studies (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).

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eTable 4 – Harmonization of Educational Attainment Across Cohorts

			Assigned Educational Category			
Country	**Study**		**Incomplete Elementary**	**Completed Elementary (and incomplete Middle Level)**	**Completed Middle (and some High School)**	**Completed High School (may or may not have completed Tertiary)**
Brazil		**Education System**	**Less than 5 years**	**5 to <9 years**	**9 to <12 years**	**12+ years**
	Bambui	**Available categories**	Illiterate; 1-3 years, 4-7 years	>=8 years	>=8 years	>=8 years
		Education in Years[a]		Available. Year data used to assign participants to these higher categories		
United Kingdom		**Education System**	**Less than <6 years**	**6 to <9 years**	**9 to <11 years**	**11+ years**
	CFAS	**Available categories**	None.			
		Education in Years	Available. Year data used to assign participants to a specific level of educational attainment using the Education System information			
Cuba		**Educational System**	**Less than 6 years**	**6 to <9 years**	**9 to <12 years**	**12+ years**
	CHAS	**Available categories**	None; Some, did not complete primary	Completed Primary	Completed Primary	Completed Secondary; Tertiary
		Education in Years		Available. Year data used to assign participants into either Complete Elementary or Complete Middle categories		
USA		**Educational System**	**Less than 5 years**	**5 to <8 years**	**8 to <12**	**12+ years**
	EAS	**Available categories**	*No categorical data applicable to these levels of education*			High School Diploma/GED Bachelors; Masters; Doctorate; Other
		Education in Years	Available. Year data used to assign participants to these levels of educational attainment			
	MOVIES	**Available categories**	<6th grade	6-9th grade	Partial high school	High School Graduate; Trade/Technical, Partial College College Graduate; Graduate/Professional
		Education in Years	Available. Used to assign participants to a level of educational attainment if categorical data missing			
	SALSA	**Available categories**	None.			
		Education in years	Available. Used to assign participants to a specific level of educational attainment using the Education System information			
France		**Educational System**	**Less than 5 years**	**5 to <9 years**	**9 to <12 years**	**12+ years**
	ESPRIT	**Available categories**	<5th Grade	5th Grade; 6th To 9th Grade	Technical 9th Grade;	College; College Graduate (including Technical); University
		Education in Years	Not available.			
Greece	**HELIAD**	**Educational System**	**Less than 5 years**	**5 to <9 years**	**9 to <12 years**	**12+ years**
HELIAD		**Available categories**	None.			
		Education in Years	Available. Used to assign participants to a specific level of educational attainment using the Education System information			
Hong Kong	**HK-MAPS**	**Educational System**	**Less than 6 years**	**6 to <9 years**	**9 to <11 years**	**11+ years**
		Available categories	None.			
		Education in Years	Available. Used to assign participants to a specific level of educational attainment using the Education System information			
Italy		**Educational System**	**Less than 5 years**	**5 to <8 years**	**8 to <13 years**	**13+ years**
	Invece.Ab	**Available categories**	None.			
		Education in Years	Available. Used to assign participants to a specific level of educational attainment using the Education System information			

South Korea	**KLOSCAD**	**Educational System**	**Less than 6 years**	**6 to <9 years**	**9 to <12 years**	**12+ years**
		Available Categories	Less Than High School Completion	Less Than High School Completion	Less Than High School Completion	High School Completion; University Degree
		Education in Years	Available. Used to assign participants into a level educational attainment below High School			
Germany		**Educational System**	**Less than 4 years**	**4 to <9 years**	**9 to <12 years**	**12+ years**
	LEILA	**Available Categories**	*No categorical data applicable to these levels of education*		Lower Secondary Education	Upper Secondary Education; Post-Secondary Non-Tertiary; Short Cycle Tertiary Education; Master Or Equivalent; Doctoral or Equivalent
		Education in Years	Available. Used to assign participants into a level educational attainment below Middle education			
Australia		**Educational System**	**Less than 7 years**	**7 to <11 years**	**11 to <13 years**	**13+ years**
	PATH	**Available Categories (PATH)**	Some Primary	All Of Primary, Some Of Secondary	Intermediate School Certificate	Five/Six Years of Secondary: Trade Certificate/Apprenticeship; Technicians Certificate/Advanced Certificate; Certificate Other Than Above; Associate Diploma; Undergraduate Diploma; Bachelor's Degree; Post Graduate Diploma/Certificate; Higher Degree;
		Education in Years	Available. Used to assign participants to a level of educational attainment if categorical data missing.			
	MAS	**Available Categories**	*No categorical data applicable to this category.*	Primary school, Incomplete High School	Incomplete High School; Incomplete High School + Certificate Diploma	Complete High School; Incomplete Tertiary; Complete High School + Certificate/Diploma; Completed Tertiary
		Education in Years	Available. Used to categorize participants with incomplete Elementary education			
Japan		**Educational System**	**Less than 6 years**	**6 to <9 years**	**9 to <12**	**12+ years**
	Tajiri	**Available Categories**	Less Than High School	Less Than High School	Less Than High School	High School
		Education in Years	Available. Used to assign participants to a specific level of educational attainment below High School			
	SGS	**Available Categories**	None.			
			Available. Used to assign participants to a specific level of educational attainment using the Education System information			
Singapore		**Educational System**	**Less than 6 years**	**6 to <8 years**	**8 to <10**	**10+ years**
		Available Categories	Less Than High School Completion	Less Than High School Completion	Less Than High School Completion	High School Completion, Technical or College Diploma; University Level
		Education in Years		Available. Used to assign participants to either Elementary of Middle education		
Spain		**Educational System**	**Less than 6 years**	**6 to <8 years**	**8 to < 10 years**	**10+ years**
		Available Categories (ZARADEMP)	None; Less Than Primary	Primary	Less Than High School	High School; College Diploma; Less Than Technical Formation; University Degree
		Education in Years	Available. Used to assign participants to a level of educational attainment if categorical data missing			

[a] For all studies, the year data was used to assign participants to the relevant level of educational attainment if categorical data was not available, or was not at a level of detail to assign participants to one of the four educational attainment categories.

Declaration of Conflict 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 Consumer 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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Steffi G. Riedel-Heller	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Susanne Roehr	Data Curation; Investigation; Writing – Review & Editing;
Alexander Pabst	Data Curation; Investigation; Writing – Review & Editing;
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Allison E. Aiello	Conceptualization; Methodology; Formal Analysis; Writing – Review & Editing;
Kristina Dang	Formal Analysis; Writing – Review & Editing;
Shuzo Kumagai	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Kenji Narazaki	Data Curation; Investigation; Formal Analysis;
Sanmei Chen	major role in the Sasaguri Genkimon Study;
Tze-Pin Ng	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Qi Gao	Data Curation; Investigation;
Ma-Shwe-Zin Nyunt	Data Curation; Investigation;
Kenichi Meguro	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Satoshi Yamaguchi	Data Curation; Investigation; Writing – Review & Editing;
Hiroshi Ishii	Data Curation; Investigation; Writing – Review & Editing;
Antonio Lobo	Resources; Supervision; Conceptualization; Methodology; Data Curation; Investigation; Formal Analysis; Writing – Review & Editing
Elena Lobo Escolar	Data Curation; Investigation; Formal Analysis; Writing – Review & Editing
Concepción De-la-Cámara	Data Curation; Investigation; Writing – Review & Editing;
Henry Brodaty	Funding Acquisition; Resources; Supervision; Conceptualization; Data Curation; Investigation; Writing – Review & Editing;
Julian N. Trollor	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Yvonne Leung	Writing – Review & Editing;
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