Journal Pre-proof

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

Steve R. Makkar (Conceptualization) (Methodology) (Formal analysis) (Writing - original draft) (Investigation) (Software) (Visualization), Darren M. Lipnicki (Conceptualization) (Project administration) (Data curation) (Investigation) (Writing - review and editing)<ce:contributor-role>Verification), John D. Crawford (Conceptualization) (Methodology) (Formal analysis) (Writing - review and editing), Nicole A. Kochan (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Erico Castro-Costa (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Maria-Fernanda Lima-Costa (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Breno-Satler Diniz (Data curation) (Investigation) (Writing - review and editing), Carol Brayne (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Blossom Stephan (Data curation) (Investigation) (Writing - review and editing), Fiona Matthews (Data curation) (Investigation) (Writing - review and editing), Juan J. Llibre-Rodriguez (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Jorge J. Llibre-Guerra (Data curation) (Investigation) (Writing - review and editing), Adolfo J. Valhuerdi-Cepero (Data curation) (Investigation) (Writing - review and editing), Richard B. Lipton (Funding acquisition) (Resources) (Supervision) (Data curation) (Investigation) (Formal analysis) (Writing - review and editing), Mindy J. Katz (Supervision) (Data curation) (Investigation) (Writing - review and editing), Andrea Zammit (Writing - review and editing), Karen Ritchie (Funding acquisition) (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Sophie Carles (Writing - review and editing), Isabelle Carriere (Writing - review and editing), Nikolaos Scarmeas (Resources) (Supervision) (Conceptualization) (Methodology) (Data curation) (Investigation) (Formal analysis) (Writing - review and editing), Mary Yannakoulia (Data curation) (Investigation) (Writing - review and editing), Mary Kosmidis (Conceptualization) (Methodology) (Data curation) (Investigation) (Writing - review and editing), Linda Lam (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Ada

Fung (Data curation) (Investigation) (Writing - review and editing), Wai-chi Chan (Data curation) (Investigation) (Writing - review and editing), Antonio Guaita (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Roberta Vaccaro (Data curation) (Investigation) (Writing - review and editing), Annalisa Davin (Data curation) (Investigation) (Writing - review and editing), Ki-Woong Kim (Funding acquisition) (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Ji-Won Han (Data curation) (Investigation) (Writing - review and editing), Seung-Wan Suh (Data curation) (Investigation) (Writing - review and editing), Steffi G. Riedel-Heller (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Susanne Roehr (Data curation) (Investigation) (Writing - review and editing), Alexander Pabst (Data curation) (Investigation) (Writing - review and editing), Mary Ganguli (Funding acquisition) (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Tiffany F. Hughes (Data curation) (Investigation) (Writing - review and editing), Erin P. Jacobsen (Data curation) (Investigation) (Writing - review and editing), Kaarin J. Anstey (Resources) (Supervision) (Conceptualization) (Methodology) (Data curation) (Investigation) (Formal analysis) (Writing - review and editing), Nicolas Cherbuin (Data curation) (Investigation) (Writing - review and editing), Mary N. Haan (Resources) (Supervision) (Conceptualization) (Methodology) (Data curation) (Investigation) (Formal analysis) (Writing - review and editing), Allison E. Aiello (Conceptualization) (Methodology) (Formal analysis) (Writing - review and editing), Kristina Dang (Formal analysis) (Writing - review and editing), Shuzo Kumagai (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Kenji Narazaki (Data curation) (Investigation) (Formal analysis), Sanmei Chen, Tze-Pin Ng (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Qi Gao (Data curation) (Investigation), Ma-Shwe-Zin Nyunt (Data curation) (Investigation), Kenichi Meguro (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Satoshi Yamaguchi (Data curation) (Investigation) (Writing - review and editing), Hiroshi Ishii (Data curation) (Investigation) (Writing - review and editing), Antonio Lobo (Resources) (Supervision) (Conceptualization) (Methodology) (Data curation) (Investigation) (Formal analysis) (Writing - review and editing), Elena Lobo Escolar (Data curation) (Investigation) (Formal analysis) (Writing - review and editing), Concepción De-la-Cámara (Data curation) (Investigation) (Writing - review and editing), Henry Brodaty (Funding acquisition)

(Resources) (Supervision) (Conceptualization) (Data curation) (Investigation) (Writing - review and editing), Julian N. Trollor (Resources) (Supervision) (Data curation) (Investigation) (Writing - review and editing), Yvonne Leung (Writing - review and editing), Jessica W. Lo (Conceptualization) (Methodology) (Writing - review and editing), Perminder Sachdev (Funding acquisition) (Resources) (Supervision) (Conceptualization) (Methodology) (Data curation) (Investigation) (Formal analysis) (Writing - review and editing), for Cohort Studies of Memory in an International Consortium, (COSMIC)

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

Running Title: Education, age, sex, ethnicity, and cognitive impairment

Steve R. Makkar[1], Darren M. Lipnicki[1], John D. Crawford[1], Nicole A. Kochan[1], Erico Castro-Costa[2], Maria-Fernanda Lima-Costa[2], Breno-Satler Diniz[3,4], Carol Brayne[5], Blossom Stephan[6], Fiona Matthews[7], Juan J. Llibre-Rodriguez[8], Jorge J. Llibre-Guerra[9], Adolfo J. Valhuerdi-Cepero[10], Richard B. Lipton[11,12,13], Mindy J. Katz[11], Andrea Zammit[11], Karen Ritchie[15,16,17], Sophie Carles[18,19,20], Isabelle Carriere[16,21], Nikolaos Scarmeas[17,18], Mary Yannakoulia[19], Mary Kosmidis[20], Linda Lam[21], Ada Fung[22], Wai-chi Chan[23], Antonio Guaita[24], Roberta Vaccaro[24], Annalisa Davin[24], Ki-Woong Kim[24,25,26], Ji-Won Han[27], Seung-Wan Suh[27], Steffi G. Riedel-Heller[28], Susanne Roehr[28], Alexander Pabst[28], Mary Ganguli[29], Tiffany F. Hughes[30], Erin P. Jacobsen[29], Kaarin J. Anstey[31,32,33], Nicolas Cherbuin[33], Mary N. Haan[34], Allison E. Aiello[35,36], Kristina Dang[34], Shuzo Kumagai[37], Kenji Narazaki[38], Sanmei Chen[39], Tze-Pin Ng[40], Qi Gao[40], Ma-Shwe-Zin Nyunt[40], Kenichi Meguro[41], Satoshi Yamaguchi[41], Hiroshi Ishii[41], Antonio Lobo[42,43], Elena Lobo Escolar[42,43], Concepción De-la-Cámara[42,43], Henry Brodaty[1,44], Julian N. Trollor[1,45], Yvonne Leung[1], Jessica W. Lo[1], Perminder Sachdev[1,44] for Cohort Studies of Memory in an International Consortium (COSMIC)

[1]   Centre for Healthy Brain Ageing, University of New South Wales, Sydney, Australia

[2]   Instituto René Rachou da Fundaçaõ Oswaldo Cruz, Rio de Janeiro, Brazil

[3]   Department of Psychiatry, Faculty of Medicine University Toronto, Canada

[4]   Geriatric Psychiatry Division, Center for Addiction and Mental Health, Toronto, ON, Canada

5   Department of Public Health and Primary Care, Cambridge University,

6   Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

7   Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

8   Finlay-Albarrán Faculty of Medical Sciences, Medical University of Havana, Cuba

9   Institute of Neurology and Neurosurgery Havana, Cuba; Memory and Aging Center, UCSF San Francisco

10   Medical University of Matanzas, Cuba

11   Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, Yeshiva University, New York City, New York, United States of America

12   Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Yeshiva University, New York City, New York, United States of America

13   Department of Psychiatry and Behavioral Medicine, Albert Einstein College of Medicine, Yeshiva University, New York City, New York, United States of America

15   Inserm, U1061 Neuropsychiatry: Epidemiological and Clinical Research, La Colombière Hospital, Montpellier Cedex 5, France;

16   Université de Montpellier, Montpellier, France

17   Centre for Clinical Brain Sciences, University of Edinburgh, UK

18   Inserm, UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Paris, F-75014 France

19   Paris Descartes University, Paris, France

20   Univ Paris-Sud, Villejuif, France

[21] Inserm, U1061 Neuropsychiatry: Epidemiological and Clinical Research, La Colombière Hospital, Montpellier Cedex 5, France

[17] 1st Department of Neurology, Aiginition Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece

[18] Taub Institute for Research in Alzheimer's disease and the Aging Brain, Gertrude H Sergievsky Center, Department of Neurology, Columbia University, New York, NY, USA

[19] Department of Nutrition and Dietetics (M.Y.), Harokopio University, Athens

[20] Laboratoty of Cognitive Neuroscience, School of Psychology, Aristotle University of Thessaloniki, Thessaloniki, Greece

[21] Department of Psychiatry, The Chinese University of Hong Kong

[22] Department of Applied Social Sciences, The Hong Kong Polytechnic University

[23] Department of Psychiatry, The University of Hong Kong

[24] Golgi Cenci Foundation, Corso San Martino 10, 20081 Abbiategrasso, Italy

[24] Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea

[25] Department of Psychiatry, Seoul National University, College of Medicine, Seoul, Korea

[26] Department of Brain and Cognitive Science, Seoul National University College of Natural Sciences, Seoul, Korea

[28] Institute of Social Medicine, Occupational Health and Public Health (ISAP), Medical Faculty, University of Leipzig, Leipzig, Germany

[29] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

[30]   Department of Sociology, Anthropology, and Gerontology, Youngstown State University, Youngstown, OH, USA

[31]   School of Psychology, University of New South Wales, Sydney, Australia

[32]   Neuroscience Research Australia, Sydney, Australia

[33]   Centre for Research on Ageing, Health and Wellbeing, College of Health and Medicine, The Australian National University, Canberra, Australia

[33]   Centre for Research on Ageing, Health and Wellbeing, College of Health and Medicine, The Australian National University, Canberra, Australia

[34]   University of California, School of Medicine, Department of Epidemiology and Biostatistics, CA, USA

[35]   Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill

[36]   Carolina Population Center, Chapel Hill, NC, USA

[34]   University of California, School of Medicine, Department of Epidemiology and Biostatistics, CA, USA

[37]   Center for Health Science and Counseling, Kyushu University, 6-1 Kasuga kouen, Kasuga City, Fukuoka, 816-8580, Japan

[38]   Faculty of Socio-Environmental Studies, Department of Socio-Environmental Studies, Fukuoka Institute of Technology,3-30-1 Wajiro-higashi, Higashi-ku, Fukuoka 811-0295, Japan

[39] Department of Epidemiology and Prevention, Center for Clinical Sciences, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjyuku-ku, Tokyo 162-8655, Japan

[40] Gerontology Research Programme, Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[41] Geriatric Behavioral Neurology, Tohoku University, Japan

[42] Instituto de Investigación Sanitaria Aragón, Zaragoza, Spain

[43] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Universidad de Zaragoza, Zaragoza, Spain

[44] Dementia Collaborative Research Centre, University of New South Wales, Sydney, Australia

[45] Department of Developmental Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Australia

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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.

Keywords:

cognitive decline; education; ageing; sex; age; ethnicity

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

8

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

9

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

11

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 (*education²*), 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

17

(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.

Declaration of Conflict of Interest

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CRediT authorship contribution statement

Author	Contribution
Steve R. Makkar	Conceptualization; Methodology; Formal Analysis; Writing – Original Draft; Investigation; Software; Verification; Visualization
Darren M. Lipnicki	Conceptualization; Project Administration; Data Curation; Investigation; Writing – Review & Editing; Verification;
John D. Crawford	Conceptualization; Methodology; Formal Analysis; Writing – Review & Editing;
Nicole A. Kochan	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Erico Castro-Costa	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Maria-Fernanda Lima-Costa	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;

Breno-Satler Diniz — Data Curation; Investigation; Writing – Review & Editing;

Carol Brayne — Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;

Blossom Stephan — Data Curation; Investigation; Writing – Review & Editing;

Fiona Matthews — Data Curation; Investigation; Writing – Review & Editing;

Juan J. Llibre-Rodriguez — Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;

Jorge J. Llibre-Guerra — Data Curation; Investigation; Writing – Review & Editing;

Adolfo J. Valhuerdi-Cepero — Data Curation; Investigation; Writing – Review & Editing;

Richard B. Lipton — Funding Acquisition; Resources; Supervision; Data Curation; Investigation; Formal Analysis; Writing – Review & Editing;

Mindy J. Katz — Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;

Andrea Zammit — Writing – Review & Editing;

Karen Ritchie — Funding Acquisition; Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;

Sophie Carles — Writing – Review & Editing;

Isabelle Carriere — Writing – Review & Editing;

Nikolaos Scarmeas — Resources; Supervision; Conceptualization; Methodology; Data Curation; Investigation; Formal Analysis; Writing – Review & Editing;

Mary Yannakoulia — Data Curation; Investigation; Writing – Review & Editing;

Mary Kosmidis — Conceptualization; Methodology; Data Curation; Investigation; Writing – Review & Editing;

Linda Lam — Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;

Ada Fung — Data Curation; Investigation; Writing – Review & Editing;

Wai-chi Chan — Data Curation; Investigation; Writing – Review & Editing;

Antonio Guaita	Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Roberta Vaccaro	Data Curation; Investigation; Writing – Review & Editing;
Annalisa Davin	Data Curation; Investigation; Writing – Review & Editing;
Ki-Woong Kim	Funding Acquisition; Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Ji-Won Han	Data Curation; Investigation; Writing – Review & Editing;
Seung-Wan Suh	Data Curation; Investigation; Writing – Review & Editing;
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;
Mary Ganguli	Funding Acquisition; Resources; Supervision; Data Curation; Investigation; Writing – Review & Editing;
Tiffany F. Hughes	Data Curation; Investigation; Writing – Review & Editing;
Erin P. Jacobsen	Data Curation; Investigation; Writing – Review & Editing;
Kaarin J. Anstey	Resources; Supervision; Conceptualization; Methodology; Data Curation; Investigation; Formal Analysis; Writing – Review & Editing;
Nicolas Cherbuin	Data Curation; Investigation; Writing – Review & Editing;
Mary N. Haan	Resources; Supervision; Conceptualization; Methodology; Data Curation; Investigation; Formal Analysis; Writing – Review & Editing;
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;

26

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;
Jessica W. Lo	Conceptualization; Methodology; Writing – Review & Editing;
Perminder Sachdev	Funding Acquisition; Resources; Supervision; Conceptualization; Methodology; Data Curation; Investigation; Formal Analysis; Writing – Review & Editing;

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28

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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.
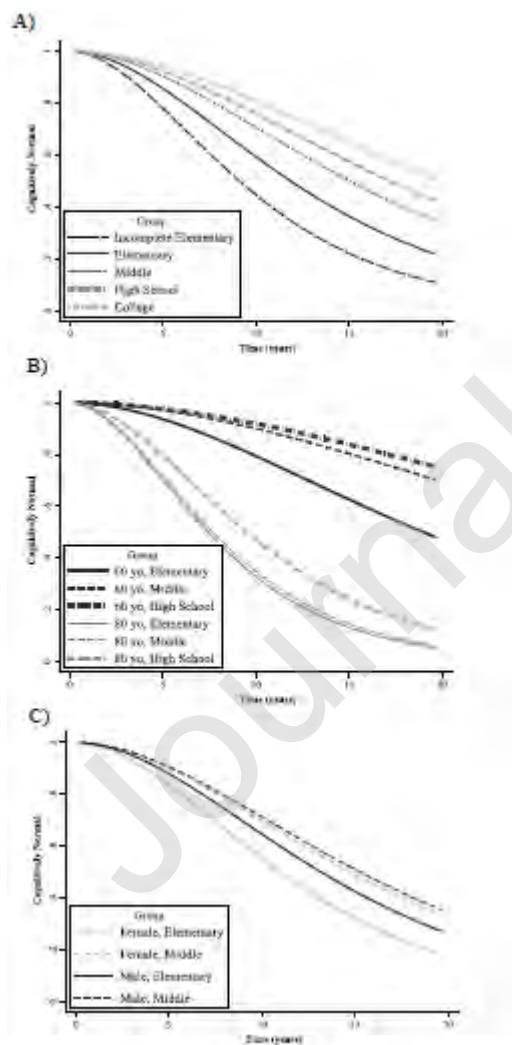
Figure 2. Ethnoregional differences in risk of cognitive impairment between education groups. A) Proportion of cognitively unimpaired White and Asian participants with an Elementary or High School education. B) Proportion of cognitively unimpaired White and Black participants with an Elementary or High School education
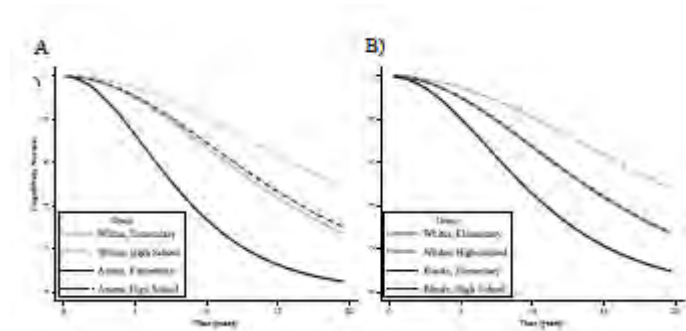
Figure 3. Interaction between educational level and carriage of *APOE*4* on the risk of cognitive impairment in ethnoregional groups. A) Proportion of cognitively unimpaired Asian *APOE*4* carriers and non-carriers with an Elementary or Middle education. B) Proportion of cognitively unimpaired White *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.
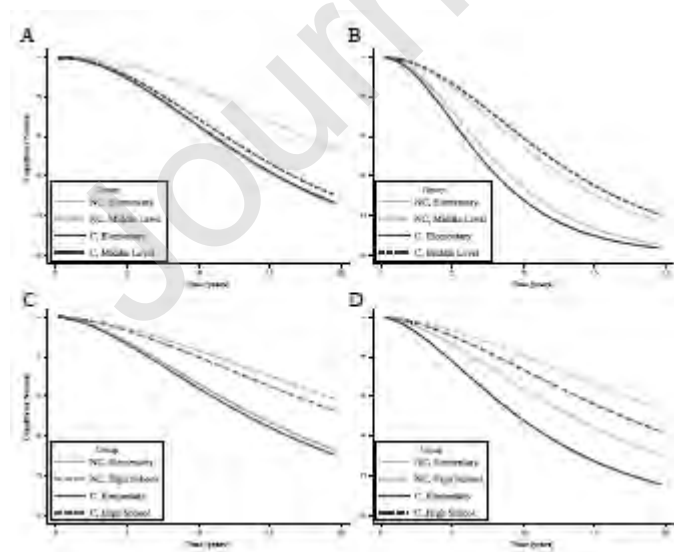
Table 1. *Descriptive Statistics of Each Included Study at Baseline*

				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.