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Education, occupational complexity, and incident dementia: A COSMIC collaborative cohort study

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Conflict of Interest
None reported.

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Abstract

Background: Education and occupational complexity are main sources of mental engagement during early life and adulthood respectively, but research findings are not conclusive regarding protective effects of these factors against late-life dementia. This project aimed to examine the unique contributions of education and occupational complexity to incident dementia, and to assess the mediating effects of occupational complexity on the association between education and dementia across diverse cohorts.

Method: We used data from 10,195 participants (median baseline age = 74.1, range = 58~103), representing 9 international datasets from 6 countries over 4 continents. Using a coordinated analysis approach, the accelerated failure time model was applied to each dataset, followed by meta-analysis. In addition, causal mediation analyses were performed.

Result: The meta-analytic results indicated that both education and occupational complexity were independently associated with increased dementia-free survival time, with 28% of the effect of education mediated by occupational complexity. There was evidence of threshold effects for education, with increased dementia-free survival time associated with 'high school completion' or 'above high school' compared to 'middle school completion or below'.

Conclusion: Using datasets from a wide range of geographical regions, we found that both early life education and adulthood occupational complexity were independently predictive of dementia. Education and occupational experiences occur during early life and adulthood respectively, and dementia prevention efforts could thus be made at different stages of the life course.

Keywords

education; occupational complexity; coordinated analysis; cognitive reserve

Introduction

Dementia currently affects more than 50 million people worldwide, and this number is expected to reach 82 million by 2030 and 152 million by 2050 [1]. Dementia leads to heavy burden for individuals, families, communities, and governments, and results in loss of well-being, quality of life, and economic productivity. Although age is the strongest risk factor for developing dementia, dementia is not an inevitable consequence of aging. Estimates suggest that 40% to 50% of dementia cases may be preventable by intervening on modifiable risk factors such as education, diabetes, midlife hypertension, mid-life obesity, smoking, depression, and physical activities [2-4]. Mental engagement during adulthood including the extent to which job behaviors and tasks require cognitive and mental efforts (i.e., occupational complexity) may also alter risk for dementia. Both education and occupational complexity are expected to be associated with lower rates of dementia [2,5-8], but not all studies have observed protective effects of education [9-12] or occupational complexity [13-16]. Moreover, reports regarding unique contributions of education and occupational complexity on incident dementia are also inconclusive [11,17-21]. The aim of the current study is to examine the associations of education and occupational complexity (i.e., mental complexity at work) with incident dementia across diverse cohorts.

A life-course approach posits that the effects of risk and protective factors act at different times over the life course [22-24]. For mental engagement, education starts to influence cognition during and after early developmental periods, and the influence of occupation typically starts during young adulthood and lasts until retirement. As educational opportunities in early life may influence or limit occupational choices later in life, the effect of education on dementia risk may be mediated, at least in part, through occupational choices, yet still both education and occupational complexity may have unique effects on dementia risk. However, there have been inconsistent findings with some studies reporting unique contributions of education [17,18] or occupation [11,18-20,25], and others failing to find independent effects [11,17,21,26]. In addition, the role of occupational complexity as a potential mediator of the association between education and dementia risk and variation in the mediation effect across countries has rarely been explored [27].

Both the cognitive reserve hypothesis [28,29] and the environmental complexity hypothesis [30,31] suggest beneficial roles that early life education and mental engagement at work during adulthood can play in preventing late-life dementia. The cognitive reserve hypothesis [28,29] proposes that various factors across the lifespan, including education, mentally engaging occupations, or high socio-economic status, serve to promote cognitive reserve in the form of better brain structure and function, and enhanced neural resources. Therefore, people with higher reserve can cope more effectively and for a longer time with brain pathology than those with lower reserve. Due to the delayed clinical expression among individuals with high versus low reserve, the risk of developing dementia would be reduced. The environmental complexity hypothesis also proposes that cognitively stimulating environments (e.g., mental activities at school or work) motivate individuals to develop their cognitive capacities [30,32]. When the mental activities from educational or occupational environments are not continued, however, the benefit in cognitive capacities may be attenuated or even lost (“Use it or lose it”).

In the current study, we used data obtained from members of the Cohort Studies of Memory in an International Consortium (COSMIC)[33]. Applying a coordinated analysis approach [34] to 7 longitudinal studies from Asia, Australia, Europe, and North America, we harmonized levels of education and occupational complexity across studies to optimize conceptual similarities of independent variables, ran identical analytic models for multiple independent datasets in order to maximize the comparability of the results, and then pooled effect sizes across independent datasets by meta-analysis. In prior studies, some used prevalent dementia cases while others used incident cases [12], making it hard to synthesize results. Thus we investigated incidence cases to better understand the etiological significance of education and occupational factors on dementia across different geographical regions. We aimed to examine whether education and occupational complexity are associated with incident dementia (i.e., dementia-free survival time) in later life, whether occupational complexity mediates the association between education and dementia, and whether there are similarities and differences across geographical regions, about which little is known [24]. From the cognitive reserve and the environmental complexity hypotheses, we hypothesized that both education and occupational complexity would be associated with reduced risks of developing dementia.

Methods

Studies and participants

The coordinated analysis included seven studies from the COSMIC collaboration [33] with at least three longitudinal assessments for dementia status and baseline data for age, sex, education, and lifetime occupational information (Table 1 lists the studies). For current study, a subsample of participants (N=10,195) from the participating studies were included in the analysis (Figure 1). Participants were excluded if they had dementia at baseline, had no follow-up, and were missing any of key variables (i.e., education, occupational complexity, baseline age, and sex). Individuals having subjective cognitive decline or mild cognitive impairment were not excluded. Because data for EAS and MYHAT were subdivided into Whites and Blacks to account for potential heterogeneity (see Analytic plans section for more information), EAS and MYHAT participants identified with races other than Whites and Blacks were excluded. The subsample of selected participants, compared to unselected participants, was more likely to have higher years of education (10 vs. 8 years, $p<.001$) and less likely to be females (58% vs. 61%, $p<.001$). There was no difference in the mean baseline age between selected and unselected participants.

COSMIC was approved by the University of New South Wales Human Research Ethics Committee. The contributing studies were approved by their respective institutional review boards, and all participants provided informed consent.

Measures

Measures of education and occupational complexity were harmonized across countries. International classification (UNESCO International Standard Classification of Education (ISCED) 1997; International Standard Classification of Occupations (ISCO)-08) provided useful frameworks for this integration (see Supplement Tables 1 and 2).

Education—Following ISCED 1997, highest degree earned was harmonized as follows defined by local standards: (i) incomplete elementary school, (ii) completed elementary school, (iii) completed middle school, (iv) completed high school, and (v) completed tertiary education, university degree, or above. For studies with minimal or no categorical education information, continuous years of education data were used to assign participants to education categories based on cut-offs specific to each country’s education system (Supplementary Table 1)[35]. Due to the irregular distribution across studies (Table 2; for example, 'Completed Elementary or below' was 0% for LEILA75+), the final education variable was coded as three levels: ‘middle school completion or below’, ‘high school completion’, and ‘above high school completion’. Note that we did not find significant differences between ‘middle school completion’ and ‘less than middle school completion’ across studies in preliminary analyses. We also used a continuous years of education variable in sensitivity analyses.

Occupational complexity—All studies provided participants’ primary lifetime occupational groups. Occupational groups were coded with different classification systems across countries as Supplement Table 2. KLOSCAD and ZARADEMP used International Standard Classification of Occupations (ISCO)-08, EAS and InveCe.Ab used occupation categories from the 1970 US Census Occupation codes, and LEILA75+, MYHAT, and SydneyMAS used their own occupation schemes that ranged 7 to 9 categorizations. These occupational groups were harmonized under one of three categories: (i) high, (ii) intermediate, and (iii) low complexity from both the *Skill level* from ISCO [36] and *substantive complexity of work* scores from the US Dictionary of Occupational Titles (DOT) [37]. *Skill level* is defined ‘as a function of the complexity and range of tasks and duties to be performed in an occupation’ [32,36,38]. Skill levels 3 and 4 involve complex problem-solving, decision-making and creativity, and require a high level of literacy and numeracy; Skill Level 2 requires relatively advanced literacy and numeracy skill; Skill Level 1 typically involves simple and routine manual tasks. *Substantive complexity of work* score is US-based occupational scores and indicates the degree to which work performance requires initiative, thought, and independent judgement involving ill-defined or conflicting contingencies [32] (see details in the below paragraph). Based on the Skill level and substantive complexity of work scores, we assigned occupational categorization of each study to one of three levels of occupational complexity. ‘High’ occupational complexity corresponds to Skill Levels 3 and 4 or high levels of substantive complexity scores; examples include managers and professionals. ‘Intermediate’ occupational complexity involves some Skill Level 2 occupational categories or medium levels of substantive complexity scores; examples include clerical and craft jobs. ‘Low’ occupational complexity involves Skill Levels 1 and 2 or lower levels of substantive complexity scores; examples include operatives (e.g., assemblers) or transport [36]. The three-level occupational complexity variable (high, intermediate, and low complexity) was used as the final occupational complexity variable.

Although we used the high/intermediate/low occupational complexity variable as a main occupational complexity variable, we conducted sensitivity analyses using the continuous, US-based *substantive complexity of work* scores from the 4th edition Dictionary of Occupational Titles (DOT; US Department of Labor) as these scores were available for several studies except for KLOSCAD and ZARADEMP. The DOT is a rich data source that contains ratings of 46 worker function and worker trait (e.g., complexity with data, etc.) for the 12,099 DOT occupation categories. Because the 46 worker variables were highly redundant, multiple-item factor scales were developed to improve reliability. To do this, data from the April 1971 Current Population Survey (CPS) [39], that contained information for 60,441 worker and were coded with both 1970 Census occupation codes and DOT occupation codes were used. Factor analysis of 46 worker function and worker trait variables using the April 1971 CPS data with the Census occupation codes resulted in four factors (substantive complexity, motor skills, physical demands, and undesirable working conditions). Ten items out of 46 worker function and worker trait variables were loaded strongly on substantive complexity of work factor: 1-3) general educational development in reasoning/mathematics/language, 4) specific vocational preparation, 5) complexity of functioning with data, 6-8) intelligence/numerical/verbal aptitude, 9) interests in abstract and creative activities, and 10) temperament for non-repetitive processes. All items were standardized and summed to form a substantive complexity scale, and for ease of interpretation, the scale was converted to a 0-10 range, with 0 representing least complexity and 10 representing the highest. In this study, five datasets (EAS, MYHAT, SydneyMAS, LEILA75+, and InveCe.Ab) provided participants' detailed occupational titles, which could be re-coded using 1970 US Census occupational codes. These Census occupation codes were linked with the substantive complexity of work scores.

Dementia diagnosis—Dementia diagnosis using DSM-IV criteria [40] were made by all studies except for MYHAT. In MYHAT, a Clinical Dementia Rating (CDR)[41] of 1.0 or above was used to indicate dementia cases, as CDR = 0 or 0.5 indicates 'no dementia' or 'questionable dementia' (equivalent to mild cognitive impairment), and CDR 1, 2, or 3 indicates 'mild', 'moderate', or 'severe dementia' [41,42]. See the references in Table 1 for diagnosis details of each study.

Other measures—Information on age, sex, race, and cardiovascular comorbidities was collected at baseline. Four studies (InveCe.Ab, MYHAT, SydneyMAS, and KLOSCAD) also provided *APOE ε4* data, which we coded as 1=carrier of one or two ε4 alleles vs. 0=non-carrier. We calculated a late-life *cardiovascular comorbidity score* as the number of four self-reported conditions: hypertension, diabetes, history of stroke or transient ischemic attack, and history of myocardial infarction (range = 0 to 4).

Analytic plans

While five studies were mostly homogeneous with respect to race, EAS and MYHAT included participants from different racial groups (28% Black for EAS; 5% Black for MYHAT). Due to potential between-race differences in educational settings, occupational acquisition, and dementia rates [21,27,43,44], we divided EAS and MYHAT into two datasets each: EAS White, EAS Black, MYHAT White, and MYHAT Black, resulting in 9 analytic datasets in total. We also conducted a sensitivity analysis using the full EAS and MYHAT cohorts.

We conducted two sets of analyses, to investigate the: 1) separate and unique effects of education and occupational complexity; and 2) mediation effects of occupational complexity on the association between education and dementia. Given a high dementia rate in LEILA75+ (22 %), we opted to use the accelerated failure time (AFT) model with a Weibull distribution rather than a proportional hazards model. Rare disease assumption is not required for causal mediation analysis under the AFT [45], and the Weibull model's assumption of monotonically increasing age-specific incidence is appropriate for dementia.

Separate and unique effects of education and occupational complexity—All main analyses were conducted using categorical education ('above high school completion', 'high school completion', and 'middle school completion or below') and occupational complexity ('high', 'intermediate', and 'low') variables. These categorical variables were harmonized using international standards across studies; in addition, because certain levels of degree earned, rather than years of education, are required to get a job, highest degree earned (categorical education) rather than years of education may be more relevant to investigate the associations among education, occupation, and dementia. Supplementary analyses were conducted using continuous education (years of education) and occupation (substantive complexity of work) variables, omitting two studies (KLOSCAD, ZARADEMP) that did not have continuous occupational complexity variables.

Under our coordinated analysis approach, we used the AFT models as described above to model the mean survival time ratio against dementia associated with education and occupational complexity in each study. Time from study entry to dementia diagnosis was used as the reference point in the AFT model for the timing of dementia. All major statistical analyses were performed using SAS 9.4 software (SAS Institute, Inc., Cary, NC). As education and occupational complexity are highly correlated, analytic models were sequentially constructed as follows: (i) education only model, (ii) occupation only model, and (iii) joint model of education and occupation. Preliminary analyses found no evidence of interaction between education and occupational complexity, so we did not include the interaction term in any model. All models controlled for sex and baseline age, then further controlled for late-life cardiovascular comorbidities. We also investigated whether APOE ε4 status and sex moderated the associations of education or occupation with dementia. To provide weighted summary effect size across all studies, we conducted meta-analysis using the SAS METAANAL Macro [46]. A random-effects approach was chosen, treating each study as a random effect, weighting studies proportionately to the inverse of the sum of the study-specific variance and the common between-studies variance. This allowed studies with precise estimates to have the greatest impact on the overall meta-analytic estimates. Heterogeneity among studies was evaluated using I^2 statistics, which is a percentage describing the proportion of variability that is due to between-study heterogeneity and not sampling error [47,48]. Values of <30%, 30% to 60%, 61% to 75%, and >75% were regarded as low, moderate, substantial, and considerable heterogeneity, respectively [48].

Mediation analysis—To examine whether occupational complexity mediated the association between education and dementia, we performed causal mediation analyses [49]. The current statistical packages for conducting causal mediation analysis [49] allow a binary exposure variable and binary or continuous mediator variables. As we did not find significant differences between 'high school completion' and 'above high school completion' (Table 3), education was binary-coded ('high school completion or above' vs. 'less than high school completion'). As we did not find evidence of non-linear association (Table 4), occupational complexity was used as a continuous variable (0=low, 1=intermediate, 2=high). The mediator was set at the level of intermediate occupational complexity.

The causal mediation analyses approach estimates two effects: natural direct effect (NDE) and natural indirect effect (NIE)(Figure 2). The *NDE* captures the effect of the education on survival time if we were to factor out the pathway from education to occupational complexity, and thus the effect of education not mediated by occupational complexity. It compares dementia-free survival time among those with 'high school completion or above' vs. 'less than high school completion' holding occupational complexity constant at the level for 'less than high school completion'. The *NIE* is the effect of education on dementia mediated by changing occupational complexity. It indicates how survival time would change if education were fixed at 'less than high school completion' but occupational complexity were changed from the level for education 'less than high school completion' to the level it would take for education 'high school completion or above'. The sum of NDE and NIE is the *total effect*, which indicates how survival time would change overall for a change in education from 'less than high school completion' to 'high school completion or above'. Finally, the *proportion mediated* is the ratio of NIE to the total effect. Because the outcome was binary, proportion mediated was calculated on the risk difference scale as follows using survival time ratios of NDE and NIE: (NDE×(NIE-1))/(NDE×NIE-1)(see [50] for details). Preliminary analyses found no evidence of interaction between education and occupational complexity, so we did not include the exposure-mediator interaction in the mediation analyses. We used SAS macro for the mediation analysis with survival data [45,49]. The direct and indirect effects were estimated on the mean survival ratio scale. Standard errors and confidence intervals were obtained via the delta method [45]. For details about the calculation of standard error of NDE and NIE, please refer to [49]. Model equations are included in Supplementary Equation 1. Mediation analysis was conducted for each dataset, followed by meta-analysis using the SAS METAANAL Macro [46].

Results

Participant characteristics among studies

Table 2 shows the sample sizes and demographic characteristics of the cohorts used. The sample sizes varied from 75 to 3,006, with an overall sample size of 10,195. Across studies, the mean age at baseline ranged between 69 years and 82 years. The proportion of females ranged from 46.5% to 73.6%. The majority educational attainment level was at least high school completion except for InveCe.Ab and ZARADEMP. InveCe.Ab, KLOSCAD, and ZARADEMP had 11% to 43% participants with incomplete elementary education. The mean years of formal education varied from 6.9 to 13.9 years. Over 50% of participants had 'low' occupational complexity in InveCe.Ab, KLOSCAD, MYHAT Black, and ZARADEMP. The average follow-up duration ranged from 3.9 to 6.4 years. Across datasets, cumulative incidence of dementia varied considerably from 3% to 22% and person-time incident rate from 6.1 to 46.7 cases per 1,000 person-years.

Effects of education and occupation on dementia-free survival time

Table 3 and Figure 3 show survival time ratio for the effect of education on incident dementia. First, we examined individual dataset-level results. Compared to those with 'middle school completion or below', individuals with 'above high school' or 'high school completion' were more likely to have greater dementia-free survival time in EAS White, EAS Black, KLOSCAD, and LEILA75+. Though non-significant, a similar direction of effect was found for most other studies except MYHAT Black and SydneyMAS. Second, the meta-analysis based on the estimates for all nine datasets showed that 'high school completion', compared to 'middle school completion or less', was associated with a 26%

increase in dementia-free survival time after controlling for baseline age and sex (Table 3, Model 1), and a 20% increase after further controlling for occupational complexity (Table 3, Model 2). 'Above high school completion', compared to 'middle school completion or less', was associated with a 27% increase in dementia-free survival time after controlling for baseline age and sex (Table 3, Model 1). The proportion of variability in the effects due to heterogeneity between studies [47] was low to moderate, with I^2 ranged from 26.7% to 58.0%.

Table 4 and Figure 4 show survival time ratio for the effect of occupational complexity on incident dementia. In individual dataset-level results, results from EAS Black and LEILA75+ showed a protective effect of high and intermediate occupational complexity, compared to low occupational complexity, on dementia-free survival time. Though mostly in the same direction, results for other studies were not significant. MYHAT Black had the smallest sample size and large CIs. The meta-analytic estimates indicated that high occupational complexity, compared to low complexity, was associated with a 23% increase in dementia-free survival time after controlling for baseline age and sex (Table 4, Model 1), and a 19% increase after further controlling for education (Model 2). Intermediate occupational complexity, compared to low complexity, was associated with a 12% increase in dementia-free survival time after controlling for baseline age and sex. High occupational complexity, compared to intermediate complexity, was associated with a 12% increase in dementia-free survival time after controlling for baseline age and sex, and a 13% increase after further controlling for education. The proportion of variability in the effects due to heterogeneity between studies [47] was low (I^2=0.4 to 19.9%), indicating relatively consistent estimates among studies. The analyses were repeated for the original (i.e., undivided by race) EAS and MYHAT datasets (Supplementary Table 3).

Sensitivity analyses

We conducted a series of sensitivity analyses. Including late-life cardiovascular comorbidities as an additional covariate did not change the results. The results also remained unchanged in separate analyses that omitted participants (1) who were primarily housewives (InveCe.Ab, LEILA75+, MYHAT, and SydneyMAS), (2) who were employed at study entry (EAS, InveCe.Ab, MYHAT, SydneyMAS, and KLOSCAD), and (3) whose working duration was less than 10 years or who retired before age 50 (EAS, MYHAT, and SydneyMAS). Because dementia diagnosis was made with DSM-IV in all studies except for MYHAT, we conducted additional analysis excluding MYHAT, and the pattern of results stayed similar.

We also tested whether the role of education or occupational complexity varied across different subgroups by including the interaction terms of sex × education, sex × occupational complexity, APOE ε4 × education, APOE ε4 × occupational complexity, and education × occupational complexity respectively in the main analysis. No interactions were significant in any analyses. The main analyses were repeated with continuous years of education and substantive complexity of work scores (Supplementary Tables 4 and 5).

Mediation analysis

We examined whether the effect of education on dementia-free survival time was mediated by occupational complexity. Results are presented in Table 5. First, we examined individual-level study results. The survival time ratio of the NIE, which refers to the effect of education on dementia-free survival time mediated through occupational complexity, was largest in EAS Black (NIE=1.22), with 50% of the effect of education mediated through occupational complexity. For most other studies, the effects of NIE were mostly in the same direction; but all NIEs failed to reach statistical significance. The meta-analytic result showed that NIE was 1.06 (95% CI=1.02 to 1.09) and the proportion mediated was 28%, suggesting that 28% of the effect of 'high school completion or above' was mediated through having higher levels of occupational complexity. It should be noted that the proportion mediated measure should only be used when total effects and indirect effects are in the same direction [49], and thus indirect effect estimate itself rather than proportion mediated should be evidence of mediation. MYHAT Black had a large negative proportion mediated (the small sample size and large CIs were noted previously), and we fit the meta-analysis after excluding MYHAT Black data but the NIE remained similar (estimate=1.05, 95% CI=1.02 to 1.09).

Supplementary analyses were conducted using continuous years of education and substantive complexity of work variables (Supplementary Table 6). We set the baseline level of education to 6 years (the sample mean) and the new exposure level was set to 9 years. The mediator was set at the level of sample mean. NIEs were not significant for any individual study or the meta-analysis, although the pattern of results was similar to the above analyses.

Discussion

We investigated whether education (usually determined early in life) and occupational complexity (from young adulthood until retirement) were associated with late-life dementia. Longitudinal data of 10,195 older adults from 9 datasets, representing 7 independent studies from 6 countries over 4 continents were used. For most datasets, education and occupational complexity showed or tended to show associations with increased dementia-free survival time. Consistent with this, meta-analysis indicated that both education (high school completion vs. middle school completion or less) and occupational complexity (high vs. low complexity) were independently associated with increased dementia-free survival time. In addition, occupational complexity showed a modest mediating effect on the association between education and dementia, with 28% of the effect of education being mediated by occupational complexity. Our finding of independent effects of both education and occupational complexity suggests the importance of maintaining cognitive stimulation/participation throughout life for lowering the risk of dementia.

Our findings are consistent with prior theories suggesting that mentally stimulating activities throughout the lifespan preserve late-life cognitive health and protect against dementia [28,32]. From the environmental complexity hypothesis, mentally challenging environments in educational or occupational settings motivate individuals to develop their cognitive capacities as long as they continue their mental activities in those environments [31,32]. In addition, the cognitive reserve hypothesis [28,29] suggests that different aspects of life experience including early life education or midlife work experiences can modulate cognitive reserve, i.e., the brain's resilience to pathology. Greater mental stimulation may prevent individuals with advanced pathology from expressing the symptoms, postpone the onset of dementia, and reduce the rates of incident dementia. Evidence from animal studies also suggests that, even in advanced age, enriched environments benefit the brain by stimulating neurogenesis and through better development and maintenance of neural connections [51-54]. In line with this evidence, we found that education and occupational complexity independently contributed to the reduced risks of developing dementia.

Although these theories focus on enrichment effects of *higher* levels of education or occupational complexity, it is also possible that resource deprivation from *lower* levels of education or occupational complexity may play a role. We found a threshold effect of education: Individuals with 'high school completion or above' compared to those with 'less than high school completion' were less likely to develop dementia, while there was no significant difference in dementia rates between 'high school completion' and 'above high school completion'. Individuals without high school diploma are likely to have a harder time to find and keep jobs [55,56] and live below the poverty line [57]. Then these individuals are at greater risk of exposure to stress (e.g., unemployment) or discrimination, which negatively influence neural mechanisms underlying cognitive function [58,59]. It would not be distinguishable whether the effects of education or occupational complexity on dementia are from cognitive enrichment or resource deprivation because these mechanisms are likely to work in parallel and influence each other to contribute to late-life cognitive health. However, all of these factors, cumulatively and interactively, would result in an "aggregate of marginal gains" and significantly impact late-life cognitive health [60,61].

One of the benefits of using the coordinated analysis approach is that it allows for the replication of research findings across independent studies and then examination of combined results. There were considerable differences in study characteristics (e.g., interval of measurement occasions, country of origin) as well as incident dementia rates, which may be attributable to baseline differences in participant characteristics such as age ranges and birth cohorts, as well as methodological differences across studies [62]. However, we were able to achieve comparability by harmonizing the key variables of education and occupational complexity, using the clinical dementia outcome, applying the same analytic model, and using identical covariates. Although some studies did not reach statistical significance, the effects of education and occupational complexity on incident dementia were in the expected direction for most datasets. There were differences in the distribution of the key variables across studies: for example, the proportion of individuals having high school diploma was low in InveCe.Ab (9.2%) and ZARADEMP (13.4%). These differences seem to contribute to the significance of the effects (i.e., large CIs)(see Figure 3). The effects of education and occupational complexity became more obvious when effects were combined by meta-analysis.

The effects of education and occupational complexity were attenuated when they were included in the same analytic model, which pointed to the need for mediation analyses. Although the high correlation and the mediating process between education and occupational complexity might have contributed to this attenuation, there might have been unmeasured shared variance that leads to confounding; shared variance may be related to premorbid intelligence or socioeconomic status and merits future investigation. The effects of education and occupation were more attenuated when these variables were parametrized as continuous variables. However, care should be taken when interpreting the results using continuous variables for the reasons listed below. Years of education may be less relevant than highest degree earned in examining the associations of education, occupation, and dementia because the latter would be important in getting a certain job and following health-related environments and consequences. We harmonized highest degree earned by the local standards due to different education systems across countries whereas years of education could not be harmonized. For occupation, it is possible that the level of mental engagement required for a particular occupation (i.e., continuous measure of substantive complexity of work scores derived from the US DOT and the US-based population survey) may differ across countries. In addition, two studies (KLOSCAD, ZARADEMP) did not have substantive complexity of work scores and thus were omitted from the meta-analysis, which would limit the generalizability.

Across datasets, the proportion of variability in the effect of education due to heterogeneity was low to moderate (27~58%). This level of variability is possibly due to various socio-cultural reasons (e.g., different effects of World War II on the education of school-age children across countries) or different educational systems. There was less variability between studies for the effect of occupational complexity across studies (0~20%) than that of education, suggesting that mental engagement reflected by occupational categorization may be more consistent across regions compared to mental engagement reflected by levels/ labels of education. A more consistent effect of occupational complexity may be associated with its proximity to the outcome (dementia), longer period of life it applies to, or critical period of life it applies to – e.g., offsetting midlife factors such as cardiovascular disease and overweight/obesity, which are known to be important risk factors of dementia [63,64].

We found a modest and partial mediation effect of occupational complexity on the association between education and incident dementia. The indirect effect was significant in the meta-analytic result, and 28% of the effect of education was mediated by occupational complexity. This finding is generally in line with a prior study [27], which found an 11~22% mediating effect of occupational complexity on the association between early life education and mid- to late-life cognitive functioning among individuals aged ≥ 45 in the US. The current finding suggests that there may be other mediating mechanisms through which education is associated with dementia, such as healthy lifestyles, access to healthcare, and reduction in midlife cardiovascular risks [12,22].

In the current analysis, studies conducted in the US (EAS, MYHAT) included racial minorities, and we stratified these datasets by race to account for population heterogeneity. Evidence from prior studies suggests that levels of cognition, dementia rates, and risk/ protective factors including educational quality and occupational opportunities differ between US Whites and Blacks [21,27,43,44,65,66]. For both EAS and MYHAT, Blacks had greater percentages than Whites of ‘less than high school completion’ and ‘low occupational complexity’. Further, the association between occupational complexity and dementia differed between Blacks and Whites in EAS, where occupational complexity predicted dementia only among Blacks. Blacks from EAS also showed the strongest mediation pattern, with 50% of the effect of education mediated by occupational complexity. Prior research found that education confers differential benefits in employment by race [67]. Employment opportunities were significantly better for Blacks with high school diploma compared to Blacks without high school diploma, and this difference in employment was greater over time than the difference between Whites with high school diploma and Whites without high school diploma. This finding suggests a stronger education–occupation link for minoritized people in US.

The effects of education and occupation remained after controlling for the late-life comorbidities, and cardiovascular comorbidities themselves did not appear to substantially contribute to the risk of dementia. Previous studies found that dementia is more associated with midlife vascular risk factors, such as obesity, hypertension, and high cholesterol, than late-life vascular factors [68,69]. There has been controversy over the moderating effects of education or occupational complexity in the associations of APOE ε4 or sex with dementia, or the interaction effects between education and occupational complexity [17,35,70-74]. We found no difference in the effects of education or occupational complexity between subgroups of sex or APOE ε4 carrier status, nor did education interact with occupational complexity.

Our findings have implications for policy to prevent dementia and reduce dementia rates. There are various factors across the life span that contribute to late-life cognition and dementia [22,24]. Specifically, education starts to influence cognition during and after early developmental periods, and the influence of occupation typically starts during young adulthood and lasts until retirement. From the current findings that education and occupational complexity are independently predictive of dementia, it seems that dementia prevention efforts can be made at any stage of the life course. This includes prioritizing early life education, and developing ways to reduce the risk of dementia in individuals with low occupational complexity.

There are some limitations to this study. First, despite including studies from Asia, Australia, Europe, and North America, we had no studies from Africa or Latin/South America, limiting the global generalizability of our results. Given that most findings from North America and Europe have been used to inform global health policy for dementia prevention [1,23], it would be crucial to examine whether results can be generalized to different geographical locations. Second, there were potentially confounding variables or unmeasured mechanisms we were unable to consider, including premorbid intelligence, midlife vascular factors, cognitive engagement in leisure activities, financial resources, access to medical care, and health behaviors [75]. Lower education or occupational complexity may be associated with behavioral risk factors (e.g., smoking) for vascular disease, that is in turn associated with an increased risk of dementia. In addition, individuals with lower education or occupational complexity may face more stress, discrimination, and environmental and physical factors such as traumatic brain injury that also increase the risk of dementia [76,77]. Other factors we were unable to test or control for include family history of dementia, parental resources, and in particular cognitive leisure activities, which are a major source of mental engagement in late life. Third, given differences in education systems, it may be prudent to instead use an estimate of quality of education (e.g., reading level, literacy)[78,79], although these measures were not available in most studies. Fourth, we did not have data to investigate how occupational complexity in different periods of the lifespan was associated with dementia risk. Fifth, household work was classified under low occupational complexity although it may include various mental activities such as managing household budget or supervising children's education. Lastly, we did not consider competing risks (e.g., death) in our analyses. However, for etiologic purposes like the current study (rather than estimating crude incidence), it is recommended that we simply treat all competing events as though the individual were right censored at the time of competing event occurs [80,81].

Conclusion

We found that both education and occupational complexity independently contributed to the risk of dementia, using a combined analysis of 9 individual datasets from 7 cohorts. There seemed to be a threshold effect in education, with increased dementia-free survival time associated with education that was high school completion or above. There was a partial and moderate mediating effect of occupational complexity on the association between education and late-life dementia, but heterogeneity existed across studies: US Blacks showed the strongest mediation pattern, suggesting that a high school diploma may be more important among US minoritized populations in getting a decent job, and eventually maintaining cognitive health in later life. Education and occupational experiences occur during early life and adulthood respectively, and dementia prevention efforts could thus be made at different stage of the life course. Policy should address the importance of early life education and focus on higher-risk groups of individuals with less than high school completion or low occupational complexity. More longitudinal studies are needed in Africa and Latin/South American countries to inform policy recommendations across the world.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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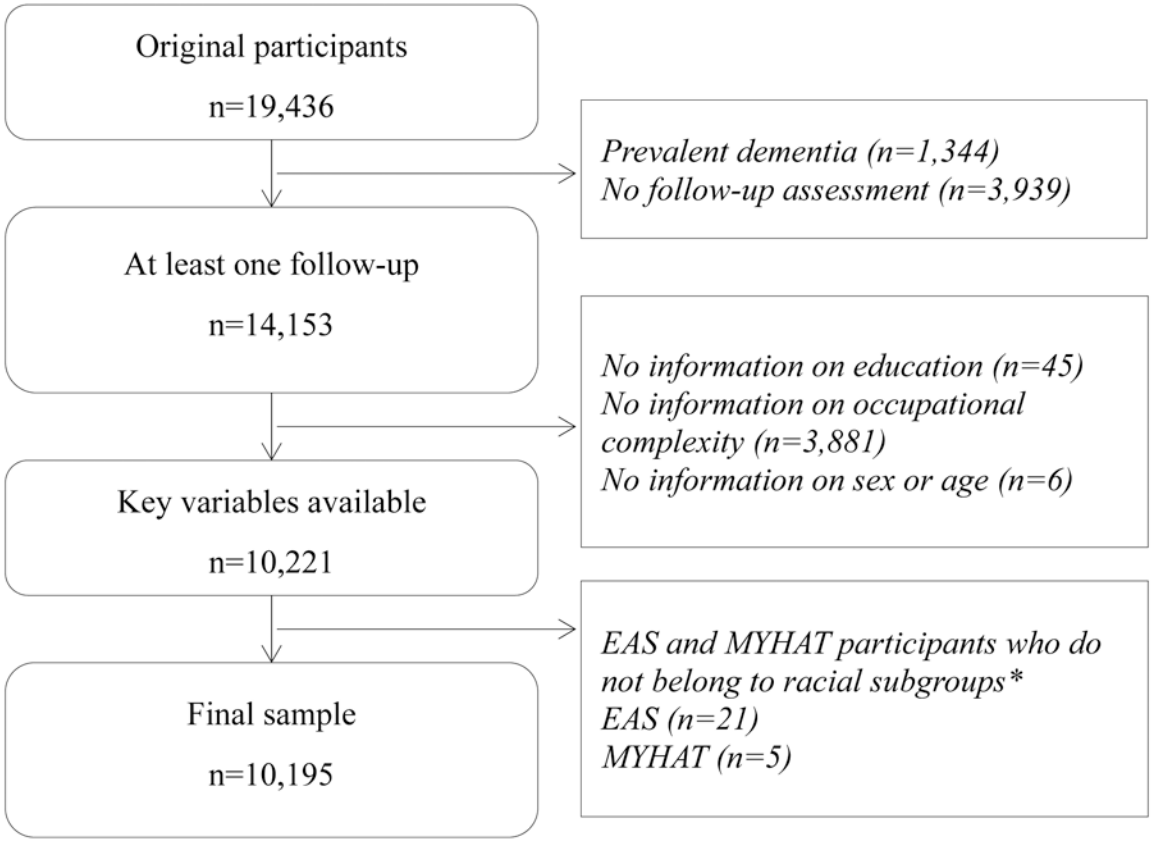

Figure 1. Sample selection.

*Data for EAS and MYHAT were subdivided into Whites and Blacks to account for potential heterogeneity; thus EAS and MYHAT participants identified with races other than Whites and Blacks were excluded.

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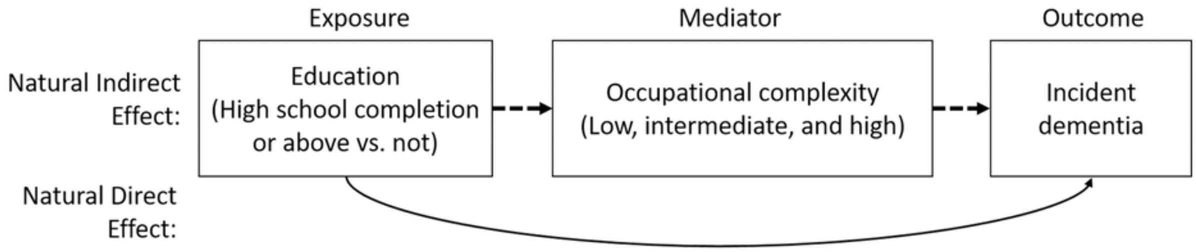

Figure 2.

The mediation model among education, occupational complexity, and dementia. The solid line indicates natural direct effect, and the dotted line represents the mediated, indirect effect. The exposure-mediator interaction was not included because results from preliminary analysis did not find evidence of interaction.

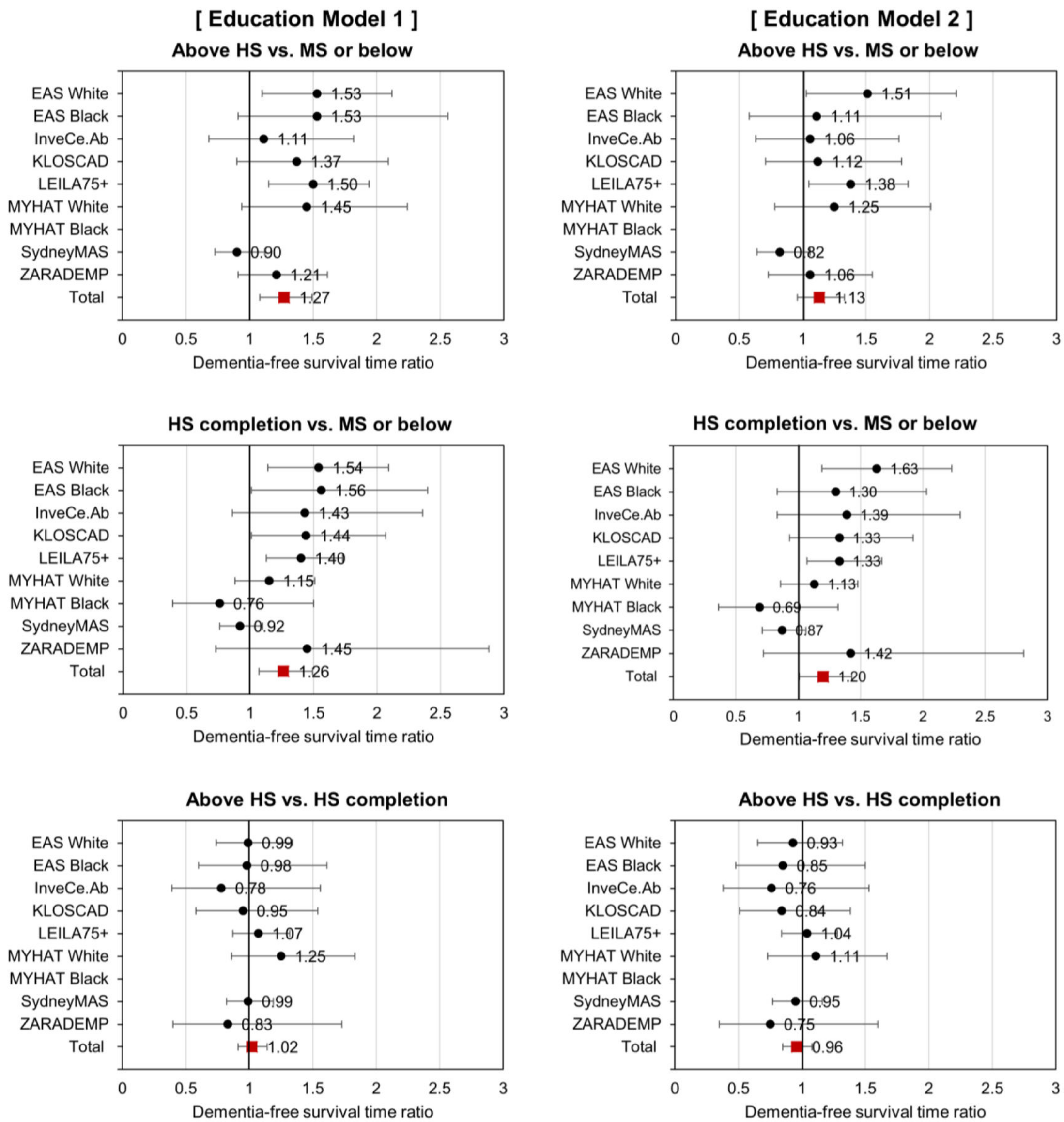

Figure 3.

Effects of education on dementia-free survival time. Model 1 controlled for sex and baseline age, and Model 2 further controlled occupational complexity. Effects were not estimated for 'Above HS' of MYHAT Black due to the insufficient sample size.

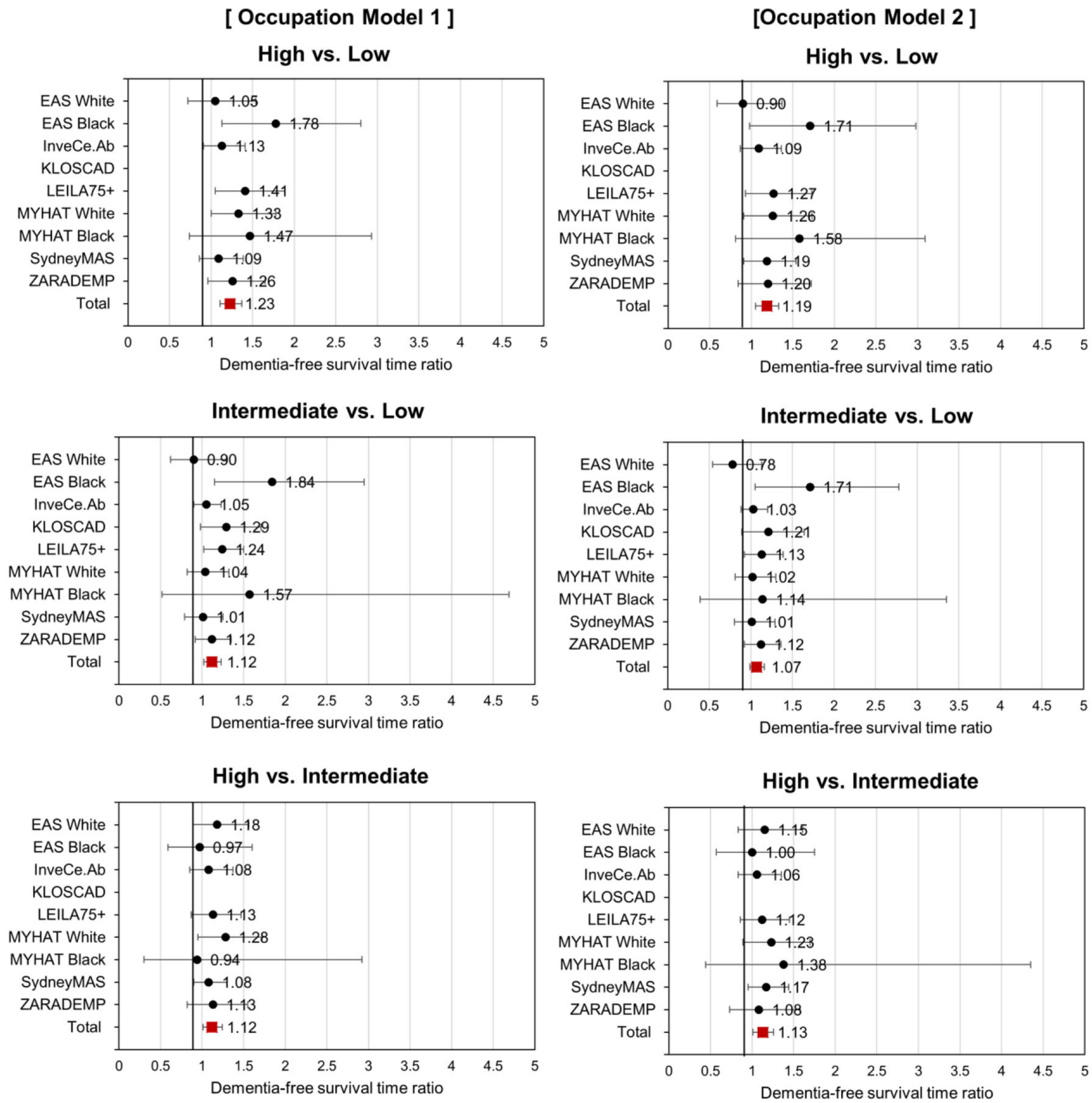

Figure 4.

Effects of occupational complexity on dementia-free survival time. Model 1 controlled for sex and baseline age, and Model 2 further controlled for education. Effects were not estimated for 'High' of KLOSCAD due to the insufficient sample size.

Table 1.

Contributing studies.

Study	Abbreviation	Location	Initial sample size	Start year
Einstein Aging Study [82]	EAS	New York, USA	2,282	1993
Invecchiamento Cerebrale in Abbiategrasso [83]	InveCe.Ab	Abbiategrasso, Italy	1,321	2009
Korean Longitudinal Study on Cognitive Aging and Dementia [84]	KLOSCAD	Nationwide, South Korea	6,809	2010
Leipzig Longitudinal Study of the Aged [85]	LEILA75+	Leipzig, Germany	1,265	1996
Monongahela-Youghiogheny Healthy Aging Team [86]	MYHAT	Southwestern Pennsylvania, USA	1,919	2006
Sydney Memory and Ageing Study [87]	SydneyMAS	Sydney, Australia	1,037	2005
ZARAgoza DEMentia DEPression Project [88]	ZARADEMP	Zaragoza, Spain	4,803	1994

Table 2.

Demographic characteristics of analytic samples from the contributing studies.

Dataset	EAS White	EAS Black	InveCe. Ab	KLOS -CAD	LEILA 75+	MYHAT White	MYHAT Black	Sydney MAS	ZARA -DEMP
N	948	372	1,089	1,485	928	1,573	75	719	3,006
Age range	66~100	66~97	70~76	59~91	75~99	65~99	65~97	70~91	58~103
Baseline age (Mean, SD)	79 (5.4)	77.3 (5)	72.6 (1.3)	68.8 (5.9)	81.5 (4.8)	78 (7.3)	76.9 (8.3)	78.4 (4.6)	71.9 (8.7)
Female %	57.1	72.6	53.6	46.5	73.6	61.7	70.7	56.5	57.4
Categorical education %									
Incomplete elementary	0.2	1.1	10.7	12.1	0.0	0.1	0.0	1.6	43.1
Completed elementary	2.1	6.5	50.1	21.2	0.0	0.4	6.7	27.2	40.0
Completed middle school	15.2	17.7	29.9	15.2	14.0	11.8	24.0	3.0	3.6
Completed high school	47.5	48.7	6.9	34.4	54.9	72.4	58.7	45.0	3.2
Above high school	35.0	26.1	2.3	17.1	31.1	15.4	10.7	23.3	10.2
Years of education (Mean, SD)	13.9 (3.5)	13.1 (3.6)	6.9 (3.3)	9.9 (4.7)	11.9 (1.8)	12.9 (2.4)	12 (2.7)	11.5 (3.5)	7.4 (3.8)
Categorical occupational complexity %									
High	41.3	40.3	14.0	1.5	19.9	31.2	28.0	51.1	11.4
Intermediate	41.3	32.3	27.6	45.1	58.7	32.3	16.0	34.0	14.1
Low	17.3	27.4	58.5	53.5	21.4	36.6	56.0	14.9	74.4
Substantive complexity of work (Mean, SD)	5.2 (1.9)	4.6 (2)	2.9 (2)	-	4.3 (2.1)	4.1 (2.2)	3.5 (2.3)	5.4 (2.2)	-
Follow-up years (Mean, SD)	4.5 (3.4)	4.7 (3.6)	3.9 (0.7)	4.9 (1.6)	4.8 (3.3)	6.4 (3.7)	6.1 (3.6)	5.2 (1.3)	4.1 (1.2)
Cumulative incident dementia %	10.8	12.6	5.1	3.0	22.0	7.1	17.3	11.0	4.4
Incidence rate per 1000 person-years	24.0	27.1	13.2	6.1	46.7	11.0	28.3	21.1	10.7

Table 3.

Effects of education (Above high school vs. High school completion vs. Middle school completion or below) on dementia-free survival time

Dataset	Levels of education	Education Model 1		Education Model 2	
		Survival time ratio (95% CI)	p	Survival time ratio (95% CI)	p
EAS White	Above HS vs. MS or below	**1.53 (1.1 to 2.12)**	**0.011**	**1.51 (1.03 to 2.21)**	**0.034**
	HS completion vs. MS or below	**1.54 (1.14 to 2.09)**	**0.005**	**1.63 (1.19 to 2.23)**	**0.002**
	Above HS vs. HS completion	0.99 (0.74 to 1.34)	0.954	0.93 (0.65 to 1.32)	0.672
EAS Black	Above HS vs. MS or below	1.53 (0.91 to 2.56)	0.11	1.11 (0.58 to 2.09)	0.758
	HS completion vs. MS or below	**1.56 (1.01 to 2.40)**	**0.043**	1.30 (0.83 to 2.03)	0.255
	Above HS vs. HS completion	0.98 (0.60 to 1.61)	0.932	0.85 (0.48 to 1.50)	0.578
InveCe.Ab	Above HS vs. MS or below	1.11 (0.68 to 1.82)	0.674	1.06 (0.63 to 1.76)	0.837
	HS completion vs. MS or below	1.43 (0.86 to 2.36)	0.164	1.39 (0.83 to 2.30)	0.207
	Above HS vs. HS completion	0.78 (0.39 to 1.56)	0.479	0.76 (0.38 to 1.53)	0.444
KLOSCAD	Above HS vs. MS or below	1.37 (0.90 to 2.09)	0.144	1.12 (0.71 to 1.78)	0.627
	HS completion vs. MS or below	**1.44 (1.01 to 2.07)**	**0.045**	1.33 (0.93 to 1.92)	0.122
	Above HS vs. HS completion	0.95 (0.58 to 1.54)	0.829	0.84 (0.51 to 1.38)	0.493
LEILA75+	Above HS vs. MS or below	**1.50 (1.15 to 1.94)**	**0.003**	**1.38 (1.05 to 1.83)**	**0.023**
	HS completion vs. MS or below	**1.40 (1.13 to 1.73)**	**0.002**	**1.33 (1.07 to 1.67)**	**0.012**
	Above HS vs. HS completion	1.07 (0.87 to 1.32)	0.526	1.04 (0.84 to 1.28)	0.739
MYHAT White	Above HS vs. MS or below	1.45 (0.94 to 2.24)	0.096	1.25 (0.78 to 2.01)	0.361
	HS completion vs. MS or below	1.15 (0.88 to 1.51)	0.292	1.13 (0.86 to 1.48)	0.377
	Above HS vs. HS completion	1.25 (0.86 to 1.83)	0.239	1.11 (0.73 to 1.67)	0.633
MYHAT Black	Above HS vs. MS or below	-	-	-	-
	HS completion vs. MS or below	0.76 (0.39 to 1.50)	0.433	0.69 (0.36 to 1.32)	0.262
	Above HS vs. HS completion	-	-	-	-
SydneyMAS	Above HS vs. MS or below	0.90 (0.73 to 1.12)	0.346	0.82 (0.64 to 1.06)	0.125
	HS completion vs. MS or below	0.92 (0.76 to 1.10)	0.346	0.87 (0.71 to 1.06)	0.164
	Above HS vs. HS completion	0.99 (0.82 to 1.19)	0.892	0.95 (0.77 to 1.16)	0.605
ZARADEMP	Above HS vs. MS or below	1.21 (0.91 to 1.61)	0.195	1.06 (0.73 to 1.55)	0.752
	HS completion vs. MS or below	1.45 (0.73 to 2.88)	0.284	1.42 (0.72 to 2.81)	0.316

Dataset	Levels of education	Education Model 1		Education Model 2	
		Survival time ratio (95% CI)	p	Survival time ratio (95% CI)	p
	Above HS vs. HS completion	0.83 (0.40 to 1.73)	0.622	0.75 (0.35 to 1.60)	0.455
Total	Above HS vs. MS or below	**1.27 (1.08 to 1.49)**	**0.004**	1.13 (0.96 to 1.33)	0.136
	HS completion vs. MS or below	**1.26 (1.07 to 1.49)**	**0.007**	**1.20 (1.01 to 1.43)**	**0.041**
	Above HS vs. HS completion	1.02 (0.91 to 1.14)	0.746	0.96 (0.85 to 1.08)	0.519

Note. Model 1 controlled for sex and baseline age; Model 2 further controlled for occupational complexity.

Effects were not estimated for 'Above HS' in MYHAT Black due to the insufficient sample size.

Table 4.

Effects of occupational complexity (high vs. intermediate vs. low) on dementia-free survival time.

Dataset	Levels of occupational complexity	Occupation Model 1		Occupation Model 2	
		Survival time ratio (95% CI)	p	Survival time ratio (95% CI)	p
EAS White	High vs. Low	1.05 (0.72 to 1.54)	0.791	0.90 (0.59 to 1.37)	0.632
	Intermediate vs. Low	0.90 (0.62 to 1.29)	0.551	0.78 (0.54 to 1.13)	0.192
	High vs. Intermediate	1.18 (0.89 to 1.56)	0.258	1.15 (0.83 to 1.61)	0.395
EAS Black	High vs. Low	**1.78 (1.13 to 2.8)**	**0.012**	1.71 (0.98 to 2.98)	0.058
	Intermediate vs. Low	**1.84 (1.15 to 2.95)**	**0.012**	1.71 (1.05 to 2.78)	0.031
	High vs. Intermediate	0.97 (0.59 to 1.6)	0.900	1.00 (0.57 to 1.75)	0.995
InveCe.Ab	High vs. Low	1.13 (0.91 to 1.41)	0.272	1.09 (0.87 to 1.36)	0.476
	Intermediate vs. Low	1.05 (0.90 to 1.23)	0.528	1.03 (0.88 to 1.20)	0.732
	High vs. Intermediate	1.08 (0.85 to 1.37)	0.550	1.06 (0.83 to 1.35)	0.656
KLOSCAD	High vs. Low	-	-	-	-
	Intermediate vs. Low	1.29 (0.98 to 1.71)	0.072	1.21 (0.89 to 1.64)	0.220
	High vs. Intermediate	-	-	-	-
LEILA75+	High vs. Low	**1.41 (1.05 to 1.89)**	**0.023**	1.27 (0.93 to 1.73)	0.135
	Intermediate vs. Low	**1.24 (1.02 to 1.50)**	**0.028**	1.13 (0.92 to 1.39)	0.231
	High vs. Intermediate	1.13 (0.87 to 1.47)	0.343	1.12 (0.86 to 1.45)	0.407
MYHAT White	High vs. Low	1.33 (1.00 to 1.78)	0.053	1.26 (0.91 to 1.73)	0.162
	Intermediate vs. Low	1.04 (0.82 to 1.32)	0.726	1.02 (0.81 to 1.30)	0.848
	High vs. Intermediate	1.28 (0.95 to 1.72)	0.109	1.23 (0.89 to 1.70)	0.212
MYHAT Black	High vs. Low	1.47 (0.74 to 2.93)	0.270	1.58 (0.81 to 3.09)	0.179
	Intermediate vs. Low	1.57 (0.52 to 4.69)	0.421	1.14 (0.39 to 3.35)	0.807
	High vs. Intermediate	0.94 (0.30 to 2.92)	0.913	1.38 (0.44 to 4.35)	0.579
SydneyMAS	High vs. Low	1.09 (0.86 to 1.39)	0.485	1.19 (0.91 to 1.54)	0.198
	Intermediate vs. Low	1.01 (0.79 to 1.28)	0.938	1.01 (0.80 to 1.29)	0.907
	High vs. Intermediate	1.08 (0.90 to 1.30)	0.420	1.17 (0.95 to 1.44)	0.144
ZARADEMP	High vs. Low	1.26 (0.96 to 1.65)	0.093	1.20 (0.84 to 1.72)	0.306
	Intermediate vs. Low	1.12 (0.92 to 1.35)	0.263	1.12 (0.92 to 1.36)	0.262

Dataset	Levels of occupational complexity	Occupation Model 1		Occupation Model 2	
		Survival time ratio (95% CI)	p	Survival time ratio (95% CI)	p
	High vs. Intermediate	1.13 (0.82 to 1.55)	0.450	1.08 (0.73 to 1.58)	0.703
Total	High vs. Low	**1.23 (1.11 to 1.37)**	**0.000**	**1.19 (1.05 to 1.33)**	**0.004**
	Intermediate vs. Low	**1.12 (1.02 to 1.23)**	**0.015**	1.07 (0.99 to 1.16)	0.099
	High vs. Intermediate	**1.12 (1.01 to 1.24)**	**0.028**	**1.13 (1.01 to 1.26)**	**0.030**

Note. Model 1 controlled for sex and baseline age; Model 2 further controlled for education.

Effects were not estimated for ‘high’ occupational complexity in KLOSCAD due to the insufficient sample size.

Table 5.

Results from causal mediation analysis with education (high school completion or above vs. less than high school completion) as an exposure variable and occupational complexity (0=low, 1=intermediate, 2=high) as a mediator variable (Survival time ratio (95% CI))

Dataset	NDE Survival time ratio (95% CI))	NIE Survival time ratio (95% CI))	Total Effect Survival time ratio (95% CI))	% Mediated*
EAS White	**1.56 (1.17 to 2.09)**	0.98 (0.88 to 1.09)	**1.53 (1.16 to 2.02)**	-
EAS Black	1.30 (0.84 to 1.99)	1.22 (0.99 to 1.52)	**1.59 (1.07 to 2.37)**	0.50
InveCe.Ab	1.26 (0.87 to 1.82)	1.03 (0.94 to 1.14)	1.30 (0.91 to 1.86)	0.14
KLOSCAD	1.27 (0.92 to 1.76)	1.11 (0.97 to 1.27)	**1.41 (1.04 to 1.92)**	0.34
LEILA75+	**1.35 (1.08 to 1.67)**	1.07 (0.99 to 1.16)	**1.44 (1.17 to 1.77)**	0.21
MYHAT White	1.13 (0.86 to 1.48)	1.06 (0.99 to 1.14)	1.20 (0.92 to 1.56)	0.34
MYHAT Black	0.74 (0.38 to 1.44)	1.18 (0.91 to 1.54)	0.87 (0.45 to 1.68)	-
SydneyMAS	0.87 (0.72 to 1.05)	1.04 (0.98 to 1.10)	0.91 (0.76 to 1.08)	-
ZARADEMP	1.13 (0.84 to 1.53)	1.10 (0.95 to 1.26)	1.24 (0.95 to 1.62)	0.45
Meta-analysis	**1.18 (1.01 to 1.36)**	**1.06 (1.02 to 1.09)**	**1.26 (1.09 to 1.47)**	0.28

NDE: Natural direct effect, NIE: Natural indirect effect.

* The proportion mediated measure should only be used when direct and indirect effects are in the same direction [49], and the proportion mediated was not presented when direct and indirect effects are in different directions.