Educational attainment genetic predispositions and its relationship with cognitive decline

Abstract

Recent studies have demonstrated a common genetic basis for educational attainment and cognitive abilities. This raises questions about whether cognitive decline in older age may be associated with genetic risk scores for education. There remains a gap in knowledge regarding whether the genetic effects on individual differences in cognition becomes more or less prominent over the life course. In this analysis of over 5,000 older adults from the Health and Retirement Study (HRS) in the U.S., we measured change in performance on global cognition, episodic memory, working memory and mental status over a 14-year period. Growth curve models are used to evaluate the association between a polygenic risk score for education and cognitive change. Using the most recent polygenic risk scores, we found that individuals with a higher genetic predisposition for educational attainment perform better across all measures of cognition in later life. Genetic predisposition to education is associated with faster decline in old age in fluid cognitive domains -- episodic memory. Educational attainment has a protective effect on crystallised cognitive domains -- attention and concentration, and mental status. These relationships are robust even after controlling for social, health and behavioural covariates. The results also revealed a suppression effect between gene and phenotype, suggesting that failure to include one may lead to the underestimation of the other.

Social scientists have demonstrated that individuals with higher levels of educational attainment in early adulthood perform better on cognitive tasks in later life (Rietvld er al., 2014; Scarmeas & Stern, 2004; Lenehan et al., 2015). Through the acquisition of knowledge and skills, education improves problem-solving and stress-coping abilities and increases one's effectiveness in using brain networks or cognitive paradigms. The empirical evidence provided by the life course perspective on whether educational level influences the trajectory of age-related cognitive decline is inconsistent, however. Some studies linking education with cognitive change in old age find that lower levels of education are associated with a faster decline of cognitive abilities (e.g. Albert et al., 1995; Lyketsos et al., 1999). Other studies contradict this evidence, suggesting that higher levels of education do not attenuate the rate of cognitive decline (e.g. Christensen, 2001; Karlamangla et al., 2009; Zahodne et al., 2011), and are even associated with a faster rate of deterioration (e.g. Alley, Suthers, & Crimmins, 2007; Proust-Lima et al., 2008). The relationship also varies by cognitive subdomains, age, race, and educational group (Lipnicki et al., 2017).

The effect of education on cognitive level and change is difficult to separate from genetic influences, yet little is understood about the complex interplay of genetics and the environment that shape one's cognition. Genetic endowments may affect individual heterogeneity in cognitive abilities and aging (Tucker-Drob, Reynolds, Finkel, & Pedersen, 2014) both independently and through interplay with the environment (Domingue, Liu, Okbay, & Belsky, 2017). For example, education and cognitive ability have been shown to share a common genetic basis (Marioni et al., 2014; Okbay et al., 2016; Rietveld et al., 2014). Hence, even when the protective effect of education on cognitive differences and decline in old age is identified, the relationship is still questionable: both education and cognitive change can be influenced by genetics (Deary, Johnson, & Houlihan, 2009). Until now, research on the education-cognitive

decline gradient has not been able to account for genetic markers and the potential heterogeneity they bring in terms of the rate of cognitive decline. A biosocial approach could help sociologists distinguish both social and genetic pathways illuminating educational influences in cognitive change in old age. The integration of genetic effects not only establishes new channels and novel findings, but also reduces the bias of past sociological research and facilitates the examination of factors that shape cognitive decline.

The main objective of this study is thus to investigate whether the genetic predisposition of education and years of education are associated with later life cognitive functions and cognitive decline independently among middle-aged and older adults in the United States. Cognition and its decline are measured both separately in the domains of episodic memory, attention and calculation, and mental status, and incorporated into an index measuring general cognition. We use polygenic scores constructed for the Health and Retirement Survey (HRS) that summarise an individual's cumulative genetic predisposition to educational attainment. The polygenic scores for educational attainment (hereafter, EA3) are constructed by adding the effect-size-weighted risk alleles across the genome associated with education based on the third and most updated educational attainment GWAS consortium paper -- Lee et al. (2018), which used data from 1.1 million participants and identified 1,271 lead genetic variants. The EA3 correlated with years of education ($\beta = 0.8$; se = 0.03) with a predictive power of 10% in our HRS sample (see supplementary material for more details). This research tackles the following three research questions: 1) How are the EA3 and educational attainment associated with level of cognitive function? 2) How does the effect of EA3 and years of education on individual differences in cognition change with age? 3) Does the relationship between genes, education, age, and cognition still holds after controlling for other social, behavioural and health factors?

We use growth curve analysis across the waves of the HRS to gain leverage on a better understanding of how genes and education operate across the life course as people age.

Education, Gene and Cognitive Decline

Cognitive ability varies among individuals across the life-span. Moreover, the within-person's sub-dimensions of cognition decline at different rates – verbal, numerical and knowledge-based abilities remain relatively stable in late-life, while other mental abilities such as memory and processing speed start to deteriorate from middle age or even earlier and at a faster rate (Mustafa et al., 2012; Nisbett et al., 2012; Whitley et al., 2016). Drawing on *Cognitive reserve theory,* education is a widely recognised cognitive reserve, which accumulates throughout the course of one's life (Opdebeeck, Martyr, & Clare, 2016; Reed et al., 2011). Cognitive reserve allows individuals to maintain optimal performance over a longer period of time and to cope more effectively with most age-related brain changes (Fratiglioni & Wang, 2007; Stern, 2012). Older individuals with greater experiential resources exhibit better cognitive functioning. Many studies have identified that educational level in early life is associated with better cognitive status in later life (e.g., Gatz et al., 2001; Seeman et al., 2005; Zahodne et al., 2011). The theory additionally recognises that the effect of education is different through sub-domains of cognition. Episodic memory as a type of fluid intelligence involves the ability to think and reason abstractly. The fluid intelligence is considered independent of pre-existing knowledge, learning and education, and tends to decline faster during the aging process. On the other hand, crystallised intelligence, such as mental status, attention and calculation, are formed through accumulating knowledge and experience. As people age and gain new knowledge and understanding, crystallised intelligence tends to increase first and decline slower (Salthouse, 2012). As a channel to gain knowledge and skills, education is expected to have a strong effect on crystallised abilities.

A genetic predisposition to educational attainment can affect all domains of cognition and their decline directly via a shared genetic basis, or indirectly through its association with childhood intelligence, education and occupation. Yet there is no clear evidence showing whether the genetic endowments are also associated with the rate of cognitive change at an old age. Revaluating the education-cognition gradient with genetic basis captured by the polygenic risk score offers a novel approach understanding the extent to which cognitive decline is influenced by educational attainment via biological mechanisms or unobservable confounders related to environmental factors. Drawing from the recent advances in socio-genomic studies and the theoretical relationship between education and cognitive performance, we hypothesise that both EA3 and the observed years of education are independently positively related to all baseline cognitive abilities in old age (Hypothesis 1).

The cognitive reserve theory provides three competing models for the relationship between education and cognitive decline. First, the active cognitive reserve hypothesis postulates that education can improve cultural competence and skills in reading, mathematics and reasoning, which reflects a more effective use of brain function and cognitive processing (Chen, Anthony, & Crum, 1999). Education also plays an indirect role in maintaining cognitive function later in life through its association with occupation and lifestyle, which are also commonly studied cognitive reserves that may result in greater mental activity in career and leisure pursuits throughout life (Andel, Vigen, Mack, Clark, & Gatz, 2006; Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). Taking types of intelligence and genetic endowments into account, we hypothesize that years of education is associated with a lower rate of decline in mental status, attention and calculation (Hypothesis 2).

On the other hand, Tucker-Drob et al., (2009) argue that if the abovementioned mechanisms between education and cognition are increasingly relied upon increasing neurobiological

deterioration, a higher level of education would not necessarily result in a shallower rate of cognitive decline. The *compensation hypothesis* (Christensen et al., 1997; Stern, 2002) suggests that if the better-educated older individuals rely on certain cognitive domains to compensate for declines in other cognitive domains, this compensatory mechanism would slow the decline until the overcompensated cognitive domains also start to deteriorate (Alley et al., 2007). When age eventually interferes with the compensation scheme, deteriorating cognitive abilities would decline faster among a better-educated older population. This can be interpreted as that individuals whose educational attainment is increasingly driven by genetic factors that through neurobiological development may experience faster cognitive decline due to overcompensation in these cognitive domains. In other words, higher genetic propensity for education may accelerate cognitive decline in fluid intelligence such as episodic memory, as this type of cognition is independent of learning and education (Hypothesis 3).

Finally, based on physiological differences, the *passive cognitive reserve hypothesis* indicates that the number of neurons and synaptic density determines our brain's ability to cope with damage (brain reserve capacity). Individuals with a larger brain reserve with more neurons and synapses are likely to sustain more cognitive damage before clinical impairments arise (Stern, 2002). A higher level of education, especially for fluid intelligence, does not help slow the rate of cognitive decline in normal aging brains, such as a decline in processing speed, but the well-educated would continue to perform at a higher level at any age due to a greater baseline brain reserve (Salthouse, Atkinson, & Berish, 2003; Tucker-Drob, 2011). Hence we hypothesize that for episodic memory, higher level of education has no effect on its rate of change (Hypothesis 4); and for crystallised intelligence, genetic predisposition of education has no effect on their rate of decline (Hypothesis 5).

[Insert Table 1]

Since general cognition is a summary variable of the abovementioned individual domains, genetic predisposition would either have no effect or accelerate the decline, and years of education would either have no or protective effect on the decline. Table 1 summarises the types of cognitive measures and hypotheses related to each of them.

Data and Methods

Data

The Health and Retirement Survey (HRS) began in 1992, and is a biennial, longitudinal survey of a nationally-representative sample of individuals and their spouses aged 50 and above. In 2006 and 2008, the HRS collected genetic (saliva) samples from approximately 84% of participants undergoing face-to-face interviews (12,507 individuals). These DNA samples were genotyped for about 2 million SNPs. This study exploits the longitudinal nature of the HRS to explore the cognitive performance trajectories among older adults in the U.S. I use eight waves of the HRS data (from 1998 to 2012). Pre-processed datasets included the user-friendly RAND HRS data files (version P) and 1998-2012 HRS Core Files. 19,341 respondents participated in the 1998 HRS survey and had at least one measure of cognitive ability in the baseline, and among these participants, 6,984 were genotyped.

Sample

In order to be able to identify a linear trajectory, 1,925 respondents whose cognitive performance was measured fewer than three times were removed (Curran, Obeidat, & Losardo, 2010). Since this study only focuses on age-related cognitive decline, I have differentiated normal cognitive functioning from impaired functioning. A composite score measuring memory and mental status has been constructed (ranging from 0 - 27). 36 respondents with a

score of less than 7 at the baseline (1998) indicated the presence of Dementia (Crimmins, Kim, Langa, & Weir, 2011). Finally, for the main analysis, only individuals from European and non-Hispanic backgrounds were included. The 5,871 remaining respondents had at least four cognitive interviews: 25% had four or less interviews, 50% had six or more interviews, providing 34,206 person-wave observations.

Dependent variables – cognitive measures

In HRS, assessment of cognitive function is based on a reduced version of the telephone interview for the assessment of cognitive status (Desmond, Tatemichi, & Hanzawa, 1994), which was derived from the Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975). The assessment has been validated for use as a screening instrument for cognitive performance. The same cognitive tests were administered during all the included waves of data collection and were used to construct cognitive trajectories for individuals on each test (Herzog & Wallace, 1997).

Episodic Memory (EM) which encodes and retrieves personally experienced events that occurred at a specific place and time (Gabrieli, 1998) was measured by immediate and delayed word recall. Respondents were read a list of ten common words (e.g. hotel, sky, water) and were then asked to recall as many of them as possible both immediately after the list was read and also several minutes later. The score records the total number of words the respondent correctly recalled at each instance and ranges from 0 to 20.

Attention & calculation (A&C) was assessed with the serial 7s subtraction test. The respondents were asked to subtract 7 from 100, and continue subtracting 7 from each subsequent number for a total of five trials. The scores record the correct number of trials

(ranging from 0-5). The serial 7s subtraction test assessed mixed abilities of attention, calculation and working memory that maintains and manipulates information using short-term memory.

Mental Status (MS) was assessed by naming the date, month, year and day of the week (ranging from 0-4), backwards counting from 20 (0-2), object naming (0-2), and naming the current president and vice president of the U.S (0-2).

Global Cognition (GC) is a summary measure of the abovementioned cognitive domains (ranging from 0-35). To provide comparability across all measurements, I rescaled individual and global cognitive variables into a corrected percentage score – based on a division by the maximum score and multiplication by 100.

Independent variable – EA3

The EA3 is based on the most recent GWAS's results excluding the HRS samples (Lee et al., 2018), from which SNP effects on years of education are obtained. Larger scores predict higher years of education and serve as indicators for a genetic predisposition to educational attainment. The EA3 was standardised for the full sample, so that effects can be interpreted as a 1 SD change relative to the sample. The relationship between the PGS scores, years of education and cognitive functions are presented in Appendix 1.

The research method using genetic data may suffer from potential selection bias, as respondents had to live until the 2006-2008 genotyping period. Of the original 37,495 respondents, 28,136 (75%) lived until at least 2006. Such selective attrition may introduce bias into analyses of the determinants of cognitive functions (Domingue, Belsky, et al., 2017). I have therefore used

inverse probability weighting to avoid mortality selection bias on the estimated association between genetic predisposition to educational attainment and cognitive decline.

Covariates

Building on previous research, we also include a range of covariates. Gender differences in cognitive abilities have been observed throughout the population. On average, older men have a better spatial ability than older women, while older women outperform men on reasoning and vocabulary abilities (Denis Gerstorf, Ram, Hoppmann, Willis, & Schaie, 2011). Finkel et al. (2003) demonstrate that women also perform better on episodic memory performance. The rate of decline is similar for both sexes, but after adjusting for the effect of education, women outperform men in processing speed, episodic memory, fluency and knowledge (Gerstorf, Herlitz, & Smith, 2006). This result suggests that women's lack of access to education earlier in life suppresses their advantage with cognitive tasks. Social engagement has been found to be a protective indicator for cognitive aging (James, Wilson, Barnes, & Bennett, 2011). A recent study from the HRS shows that the social engagement index, taking into account marital status, participation in volunteering work and social interaction is significantly associated with better mental status and self-rated health in later life. However, the same analysis did not find evidence of any impact of the level of social engagement on patterns of cognitive decline over time (Nelson, Noonan, Goldberg, & Buchwald, 2013). Being married or cohabiting with someone and frequently interacting with other people may stimulate cognitive functions and protect the brain from deterioration (van Gelder et al., 2006). The loss of a partner could result in changes in health behaviour such as stress-induced smoking and drinking, and eventually cause adverse health and cognitive outcomes (Vidarsdottir et al., 2014). Krueger et al (2009) found that a higher level of social interaction in old age is associated with better cognitive performance in general, but this association varies across subdomains. Social engagement has

a significant effect on fluid intelligence, but not on crystallised abilities. This body of research underlines the potentially vital importance of social engagement for good cognitive functioning in later years (Ertel, Glymour, & Berkman, 2008). We measure social engagement by an index similar to the one used by Nelson, Noonan, Goldberg, and Buchwald (2013). It consists of measures for marital status, volunteering activities, and contact with family and neighbours. Respondents received one point each for: 1) being married; 2) volunteering for religious, educational, health-related, or other charitable organisations at least one hour in the past year; 3) contacting parents weekly or more frequently; 4) contacting offspring weekly or more frequently; and 5) meeting with neighbours weekly or more frequently. The index score ranges from 0 to 5. The sample was categorised into low (scores 0-1), moderate (scores 2-3), and high (scores 4-5) levels of social engagement.

A large body of research on older adults has documented that smoking increases the risk of cognitive decline (Hebert et al., 1993; Ott et al., 2004; Plassman, Newman, Welsh, Helms, & Breitner, 1994). Small or moderate alcohol consumption by older individuals is associated with better cognitive outcomes (Baumgart et al., 2015). In addition, a higher level of genetic predisposition to educational attainment is associated with higher parental social economic status (Domingue et al., 2015), which may bring a positive influence on children's health behaviours and lifestyles. Behavioural risk factors are measured by a binary variable of the respondents' current smoking status, and alcohol consumption (number of drinks per day). Alcohol consumption is divided into non-drinkers (0 drinks per day), moderate drinkers (1-3 drinks per day), and heavy drinkers (4 or more drinks per day).

Several chronic health conditions have been identified as predictors of adverse cognitive performance, including heart disease, stroke, hypertension, and diabetes. Chronic diseases related to physiological change affecting brain function may explain the association (Qiu &

Fratiglioni, 2015). Health risk indicators are measured by determining whether the respondent had ever had heart disease, diabetes, stroke or hypertension. The summarising scores were then divided into three groups: no condition (count = 0), few conditions (count = 1, 2); many conditions (count = 3, 4).

We also control for population stratification, as the frequencies of certain genetic variants vary by ancestral background. Ignoring genetic variation due to ancestry may result in population stratification bias when genetic effects are confounded by ancestry. The standard practice to account for population stratification using GWAS data is to include as covariates the first few principal components that capture most of the genetic variation due to ancestry. We adjusted the first 10 principal components for population stratification (Price, Patterson, & Plenge, 2006).

Analytical Strategy

Growth curve models were used to examine the individual cognitive trajectories of the respondents, which enabled us to study the effect of genetic predisposition to educational attainment on the baseline level of cognitive ability and on its rate of change. We fit a linear, age-related decline random effect model and allow the age intercept and slope in the models to co-vary. Separate growth curve models were estimated with each cognitive measure as a dependent variable. Random effects included intercept and linear age, with the conventional unstructured covariance. A general specification of the model is

$$Cognition_{ij} = \beta_0 + \beta_1 \times Age_j + \beta_2 \times EA3_i + \beta_3 \times EA3_i \times Age_j$$

$$+ \beta_4 \times Years\ of\ Education_i + \beta_5 \times Years\ of\ Education_i \times Age_j$$

$$+ \beta_6 * X_{ij} + \beta_7 * X_{ij} * Age_j + \mu_{ij} + \mu_{ij} * Age_j + \varepsilon_\iota$$

where $Cognition_{ij}$ represents the cognitive score for person i at age j, β_0 is the population mean of cognitive ability at baseline, β_1 represents the linear fixed effect of age, β_2 represents the effect of EA3 on the baseline cognitive ability (Age is centred at 67), β_3 is the linear effect of EA3 on the change rate of cognitive skills, β_4 and β_5 are the effects of Education, β_6 and β_7 are the effects of X – a vector including individual covariates – on the initial cognitive abilities and the growth rate of change. $\sigma_1$and σ_2 are the random intercept and slope. $\mu_{ij}$and μ_{ij} are intercept and age variance.

Results

The mean age at the sample's baseline was 67, we hence centred age at this mean for the following analyses. The rescaled cognitive scores represent the comparable percentage of correctly completed tasks. A&C and MS tasks were relatively easier compared to EM tasks. Older adults on average competed 90% and 80% of the A&C and MS tests respectively, while EM has only a mean score around 55, dragging GC towards 70 (Table 2). The trend in cognitive change over age (Figure 1) reflects that though cognitive measures all decline during later life, EM declines relatively faster than other sub-domains.

[Insert Table 2]

[Insert Figure 1]

Higher genetic predisposition for education is associated with better cognitive performance, independent of education

Figure 2 depicts the intercept results from the growth curve models on each cognitive measures. For each outcome, we explore three models – model with educational attainment only (Model Education), model with EA3 only (Model EA3), and joint model with both years of education and EA3 (Model EA3 + Education). Age, gender and the first ten principal components are included in the models (for full results, see supplementary materials).

[Insert Figure 2]

There is a clear pattern showing that both EA3 and years of education are independently positively correlated with baseline cognitive levels (Hypothesis 1). Since EA3 and educational attainment are correlated (ß = 0.31, $p < 0.001$), unsurprisingly both their effect sizes drop, yet still highly significant in the joint models. Years of education has a higher effect size than EA3 on every cognitive measures, indicating that the actual educational attainment plays a more important role than genetic predisposition on cognitive performance. A&C are the most influenced cognitive outcome by educational attainment and EA3. One standard deviation increasing in years of education and EA3 results in a 7% and 4% growth in A&C performance, respectively.

The effect of EA3 and educational attainment on cognitive decline varies over age and by domains

Figure 3 summarises the slope results from the growth curve models. EA3 and years of education influence different subdomains in cognitive decline. Years of education is independently associated with slower rate of cognitive decline in A&C and MS models (ß ≈

0.1, p<0.001), providing supporting evidence for Hypothesis 2: active cognitive reserve. Educational attainment shows a negative relationship with EM decline (p<0.1) in the education only model. After adjusting for EA3, education loses its significance on EM decline (Hypothesis 4: passive cognitive reserve).

[Insert Figure 3]

On the other hand, EA3 is found to be negatively associated with EM decline, indicating that that higher EA3 would lead to a faster rate of EM decline in old age. This finding is in line with our Hypothesis 3: compensation. For crystallised intelligence of A&C and MS, we find no evidence that EA3 is related to their rate of change, supporting Hypothesis 5: passive cognitive reserve.

For GC, we found that educational attainment is associated with GC rate of decline at the 0.1 level in the education only model. In the EA3 only model, EA3 does not have a significant effect on GC decline. Surprisingly, when both EA3 and educational attainment are included in the model, their effect both become stronger and significant at the 0.01 level. EA3 is associated with a faster GC decline driven by EM, whereas years of education is associated with a slower GC decline driven by the two crystallised cognitive functions. The GC results indicate a suppression effect between EA3 and educational attainment, that statistical removal of the EA3 effect on years of education could increase the magnitude of the relationship between years of education and cognitive decline (or vice versa).

To illustrate these trajectories, Figure 4 displays estimates age-specific cognitive scores on the basis of fixed effects of EA3. Individuals with higher EA3 scored higher on GC and EM at the late stage of middle age, but they also experienced a more rapid rate of decline than respondents with a lower level of EA3. The advantage of a higher EA3 on GC and EM fades at old ages.

For crystallised intelligence, higher EA3 does not change the rate of cognitive decline. Figure 5 shows age-specific cognitive score on the basis of fixed effects of years of education received. Years of education has a protective effect on the decline of A&C and MS, but has little effect on GC and EM.

[Insert Figure 4]

[Insert Figure 5]

The effect of EA3 and education on EM, A&C and MS holds even after controlling for covariates

Next we examine whether the effect from EA3 and years of education could be mediated by covariates. We add social engagement, drinking, smoking and health conditions individually to the joint education and EA3 models. A final full model includes all the covariates. Intercept results for EA3 and years of education are presented in Figure 6, and slope results are presented in Figure 7.

[Insert Figure 6]

[Insert Figure 7]

Effects of EA3 and years of education on baseline cognitive performance does not change after adjusting for covariates across all measured cognitive sub-domains. In the covariates adjusted models, years of education robustly predicts slower rate of A&C and MS decline, and EA3 robustly predicts faster rate of EM decline. For general cognition, we found that the effect of EA3 becomes insignificant on the rate of decline after including smoking and pre-existing

health conditions. Health conditions also confound the relationship between years of education and rate of decline together with heavy drinking.

Gender, Social Engagement, Health Behaviour and Health Condition on Cognitive Ability

Figure 8 contains detailed results from the full models with EA3, years of education and all the covariates. Gender, lifestyle and health conditions are also related to the baseline cognitive score and rate of decline. In line with previous research, we found that women had a higher baseline score on GC and EM by 4% and 7% respectively, but lower scores on A&C by 5%. History of multi-morbidity is related to lower baseline scores on EM. Smoking is related to adverse initial results in GC, A&C and especially in MS. Social engagement and drinking is not related to better cognitive performance.

[Insert Figure 8]

In terms of other sources of variance in the rate of cognitive change, gender is a significant predictor of cognitive change in all four cognitive measures, such that cognitive decline occurred at a faster rate in women. The result is in line with previous studies using HRS (Alley et al., 2007). Social engagement has a persistent protective effect on cognitive decline of three cognitive tasks. Individuals with a high level of social interaction experience a slower decline in GC, EM and MS relative to individuals with a low level of social interaction. No social engagement differences were present in the rate of decline on A&C. Mild drinking attenuates the rate of decline in all the cognitive measures, and heavy drinking is associated with slower rate of decline in MS and GC, compared with that of non-drinkers. This relationship may be related to the correlation between drinking and socioeconomic status. Those who drink may have represented a population with higher social status and social engagement, and thus a

healthier population. Finally, a higher number of existing chronic health conditions greatly accelerates cognitive decline across all cognitive measures.

Discussion

In this study we try to explain the interpersonal variability in age-related cognitive decline with genetic predisposition for educational attainment. Existing research predominantly focuses on quantifying genetic and environmental components of variance in cross-sectional cognitive data and has provided evidence of genetic influences on cognitive ability (Davies et al., 2016; Rietveld & Webbink, 2016), yet few researchers have examined longitudinal cognitive change and genetic predisposition. Genes are inherited pre-birth and remain the same over a lifespan, but genetic effects on phenotypes can vary over age as a function of gene expression associated with developmental timing or environmental circumstances (Lee, Gatz, Pedersen, & Prescott, 2016). Research to date has not offered information on changes in the genetic contribution to individual heterogeneity in cognitive performance in older age.

Our main research question is whether genetic predisposition for educational attainment and educational attainment are associated with higher initial level and variation of cognitive abilities at the early stages of older adulthood. We analysed data on the trajectory of cognitive performance across three individual and one aggregate domains in over 5,000 individuals interviewed longitudinally as part of the HRS. In line with previous literature, we find that genetic predisposition for education and educational attainment both predict higher initial level of cognitive performances. In terms of rate of cognitive change, gene and education affect different domains.

Results across a range of cognitive domains suggest that the polygenic score of education is related to a significantly higher baseline (age at 67) cognitive function. Even after controlling

for observed years of education, the relationship between education-associated genetic variants and cognitive ability still persists. These results are consistent with the evidence from Okbay et al. (2016), Rietveld et al. (2013) and Rietveld et al. (2014) that there is common genetic basis between educational attainment and cognitive ability. The shared genetic variants are associated with a particular neurotransmitter pathway involved in synaptic plasticity, which is the main cellular mechanism for learning and memory.

The analysis of cognitive trajectories caused by normal aging showed that the polygenic score of education is related to the rate of cognitive decline, but the effect is only on episodic memory – a type of fluid intelligence, and driving the same effect on global cognition. Performances in global cognition and episodic memory are better in groups with higher polygenic scores for those under 85 years old, this difference is completely attenuated over the age of 90 due to faster cognitive decline in high EA3 group.

The findings on cognitive decline are in agreement with recent studies showing that genetic effects vary in cognition with age (Lee et al., 2016). In addition, several studies have reported evidence toward the compensation hypothesis that faster cognitive decline in high education groups compared to the cognitive decline in low education groups (Gottesman et al., 2014; Karlamangla et al., 2009; Rusmaully et al., 2017). The finding that a higher genetic predisposition to educational attainment is associated with a faster rate of cognitive decline might reflect the transience of global cognition and episodic memory gains associated with this genetic predisposition, which is lost as individuals age. Genetic predisposition for educational attainment is not associated with the rate of change in working memory and mental status, supporting the passive cognitive reserve hypothesis. After adjusting for environmental covariates, the link between genes and episodic memory still hold, whereas the effect of genes

on global cognition disappeared, suggesting that age-related cognitive decline is still mainly determined by socioeconomic, life style and health factors.

Years of education also as expected strongly and robustly predicts higher level of baseline cognitive function. We found no evidence that educational attainment is associated with decline in general cognition and episodic memory, but strong evidence that the effects of education on attention and concentration, and mental status become more important over age. Our results are in line with previous findings that fluid intelligence gains little from learning and education, whereas crystallised intelligence is highly dependent on learning experience.

For global cognition, when model polygenic score for education and educational attainment separately, both polygenic score and education do not have any effect on the rate of cognitive decline. When EA3 and years of education are jointly included in the model, EA3 and years of education become both statistically significant with opposite but larger magnitude of effects. This finding indicates that polygenic score and phenotype confound each other via a suppression effect. Failure to take genetic predisposition into account may underestimate the protective effect from years of education, and the negative effect from genes for education.

Our study suffers from two main limitations. First, the variability in the genetic effect may be due to ceiling and floor effects inherent in cognitive measures that narrow the potential range of decline. Mental status as a crystallised intelligence tends to start declining at a later age compared to fluid intelligence, and is most pronounced in older adults with pathological brain damages (Albert, 1995). The findings that older adults with a lower level of genetic predisposition to educational attainment experience a more rapid cognitive decline compared to a more gradual decline for those with higher level of PGS, could be due to ceiling effects in the measurement that limit the variability of change for well-educated older adults with higher

initial scores. People with higher PGS thus enjoy higher cognition for their entire adult life. More sensitive measures that cover greater variability in cognitive function might provide more accurate estimates in future research. Sensitivity analyses excluding the individuals who scores the lowest 5% in each measure retained similar results, suggesting floor effects do not challenge the analysis.

Second, the study is based on largely homogeneous groups of non-Hispanic Caucasian older adults in the U.S. The findings may not extend to individuals of other ethnic or cultural backgrounds, or later-born cohorts. However, this limitation is ameliorated by including African-American respondents in the sample in the sensitivity analyses. The effects size of PGS shrank in models including both Caucasian and African-American respondents, mainly due to the reduced predictive power of PGS on educational attainment for African-American older adults. But the directions of the coefficients are largely in line with the main analyses, alleviating some of the concerns about the generalisability of the findings.

Despite its limitations, this study provides an important contribution to the existing knowledge about the variability of cognitive decline by genetics. The associations between a genetic predisposition to educational attainment and cognitive decline that have been identified are especially relevant because it helps clarifying the contributions of observed education and genes to cognitive aging. Future research should also consider genetic effects when tapping on non-genetic factors in cognitive decline. The finding that the effect of genetic predisposition for educational attainment on cognition declines for fluid intelligence represents a need to understand the mechanisms between genetic endowment of educational attainment and cognitive decline from a biological angle.

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Table 1. Three hypotheses on the relationship between years of education, genetic endowments and individual cognitive domains.

Cognitive Domains	Type	Relationship with higher genetic predisposition	Relationship with more years of education	Measurement
Episodic Memory	Fluid	Faster decline (Compensation)	No association (passive)	Immediate and delayed word recall
Attention and Calculation	Crystalized	No association (passive)	Slower decline (active)	Serial 7s subtraction
Mental Status	Crystalized	No association (passive)	Slower decline (active)	Object, president/vice president, and date naming
General Cognition	Both	Faster decline/ no association	Slower decline or no association	A summary variable including all three measurements above

Table 2. Baseline Descriptive Statistics

Variables	Mean (SD) or Percentage
Outcomes: Cognitive Functions (rescaled)	
EM	56.13 (16.62)
A&C	79.60 (27.30)
MS	90.85 (10.85)
GC	69.46 (11.15)
Exposure:	
EA3 (Unstandardized)	-0.24 (0.14)
Years of Education (Unstandardized)	12.96 (2.51)
Age	66.73 (6.90)
Gender (female)	58.26%
Social engagement	
Low	83.12%
Moderate	15.18%
High	1.7%
Current Smoker	18.84%
Drinking	
Non-Drinker	63.49%
Moderate-Drinker	35.37%
Heavy-Drinker	1.14%
Chronic Conditions	
No Condition	68.31%
Few Conditions	30.55%
Many Conditions	1.14%

Figure 1. Mean Trajectory over Age for Cognitive Measures (with Standard Deviation)

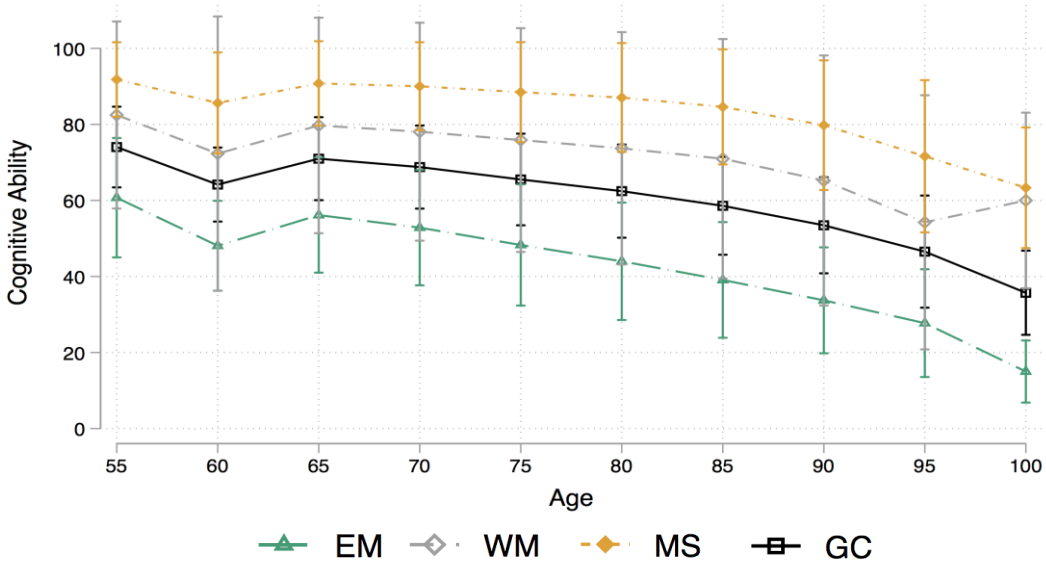
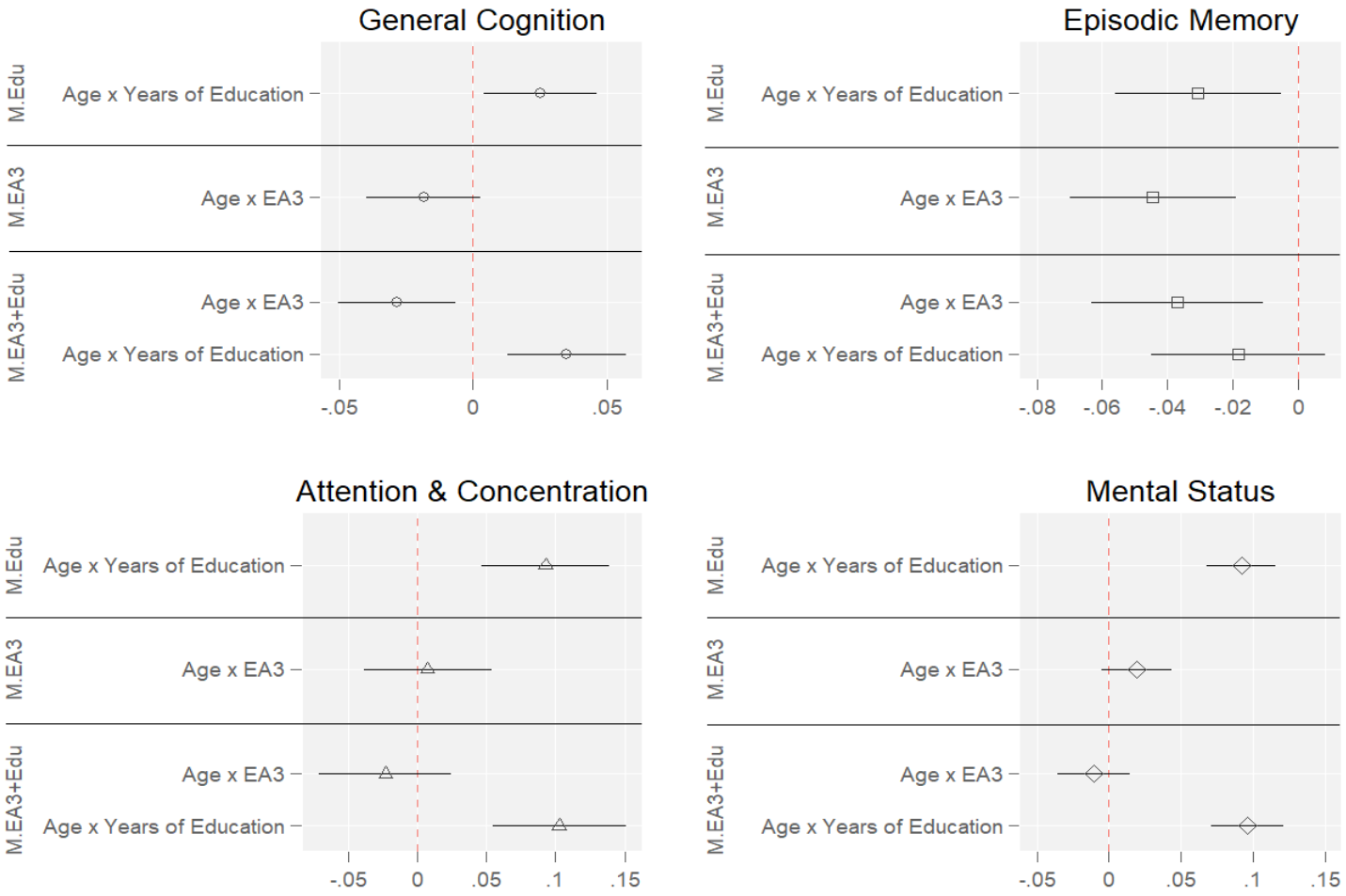


Figure 2. Intercept results from growth curve models on cognitive outcomes, with genetic risk score and years of education as predictors.

Note: EA3 and Years of education are standardised. Gender and 10 principal components are adjusted. 95% Confidence interval.

Figure 3. Slope results from growth curve models on cognitive outcomes, with genetic risk score and years of education as predictors.



Note: EA3 and Years of education are standardised. Gender and 10 principal components are adjusted. 90% Confidence interval.

Figure 4. Predicted trajectories for low and high EA3.

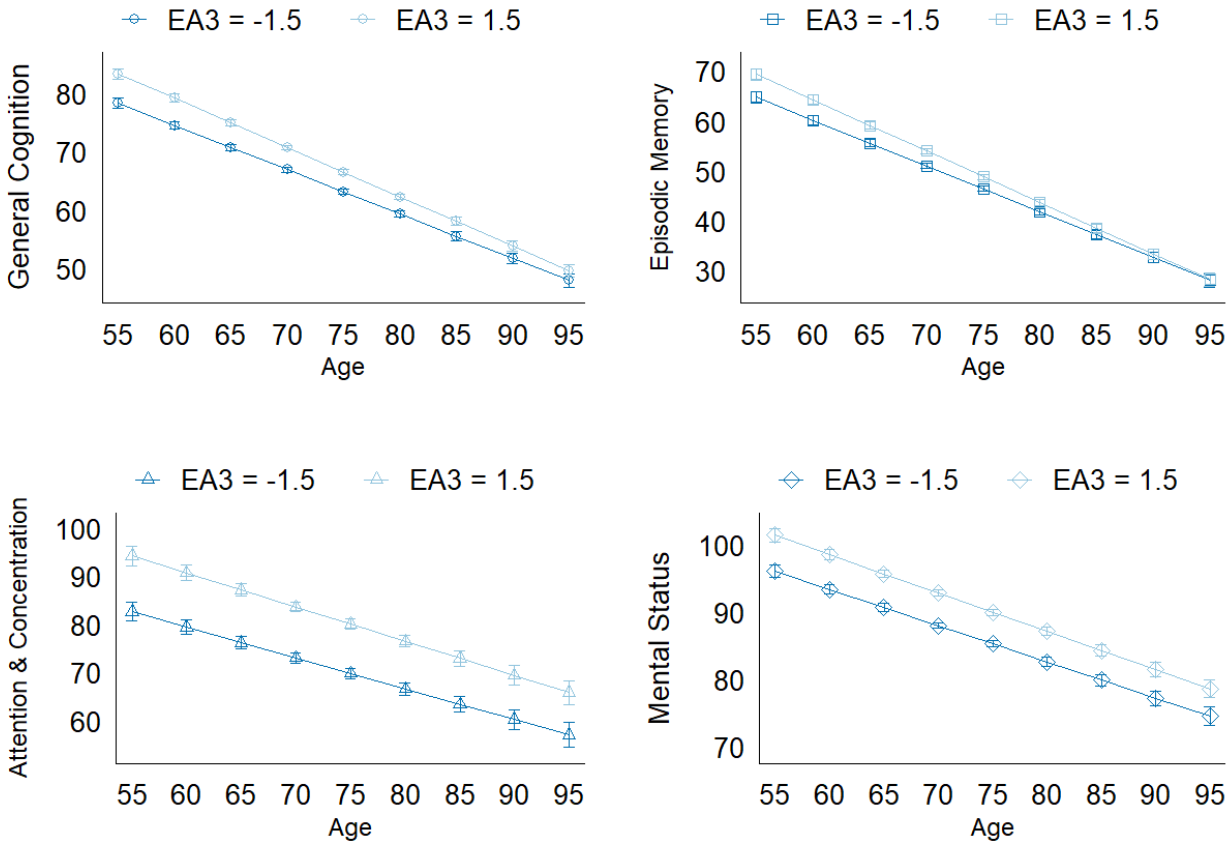


Figure 5. Predicted trajectories for low and high educational attainment.

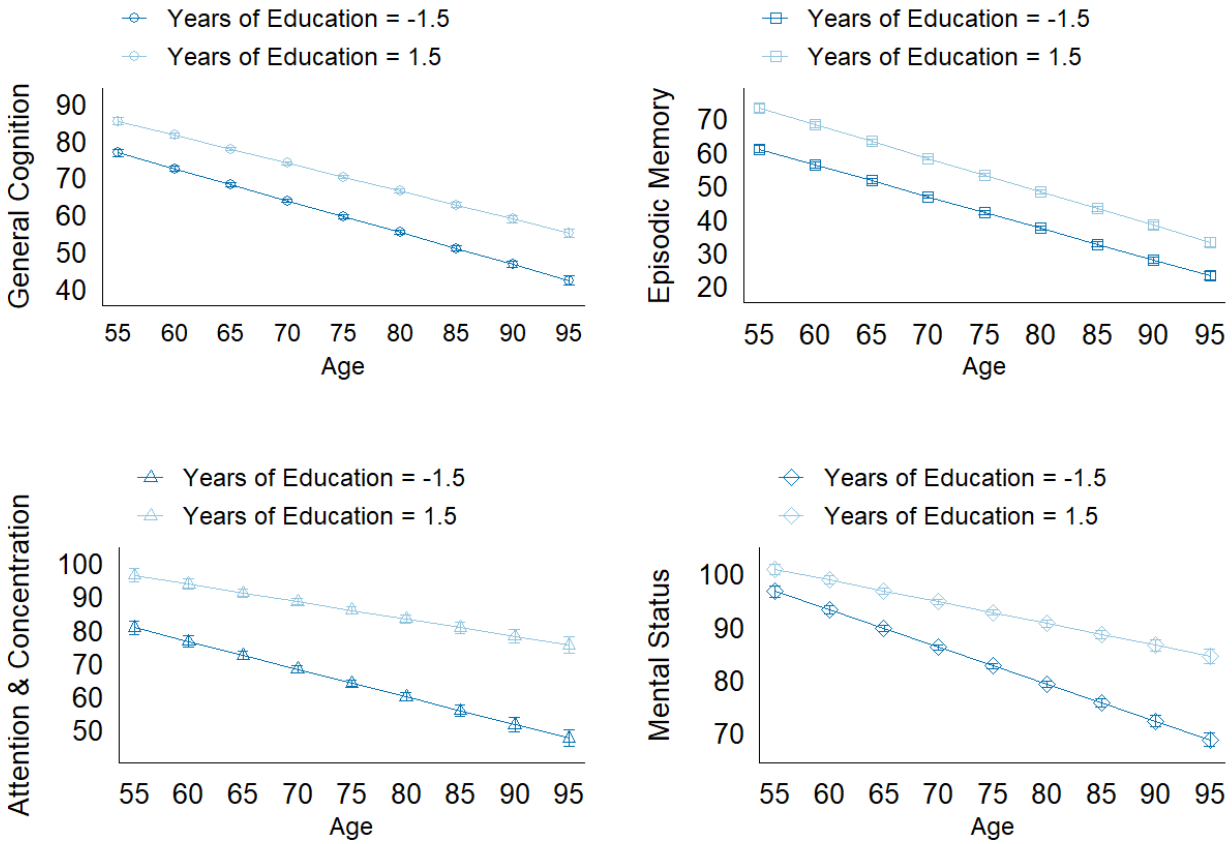
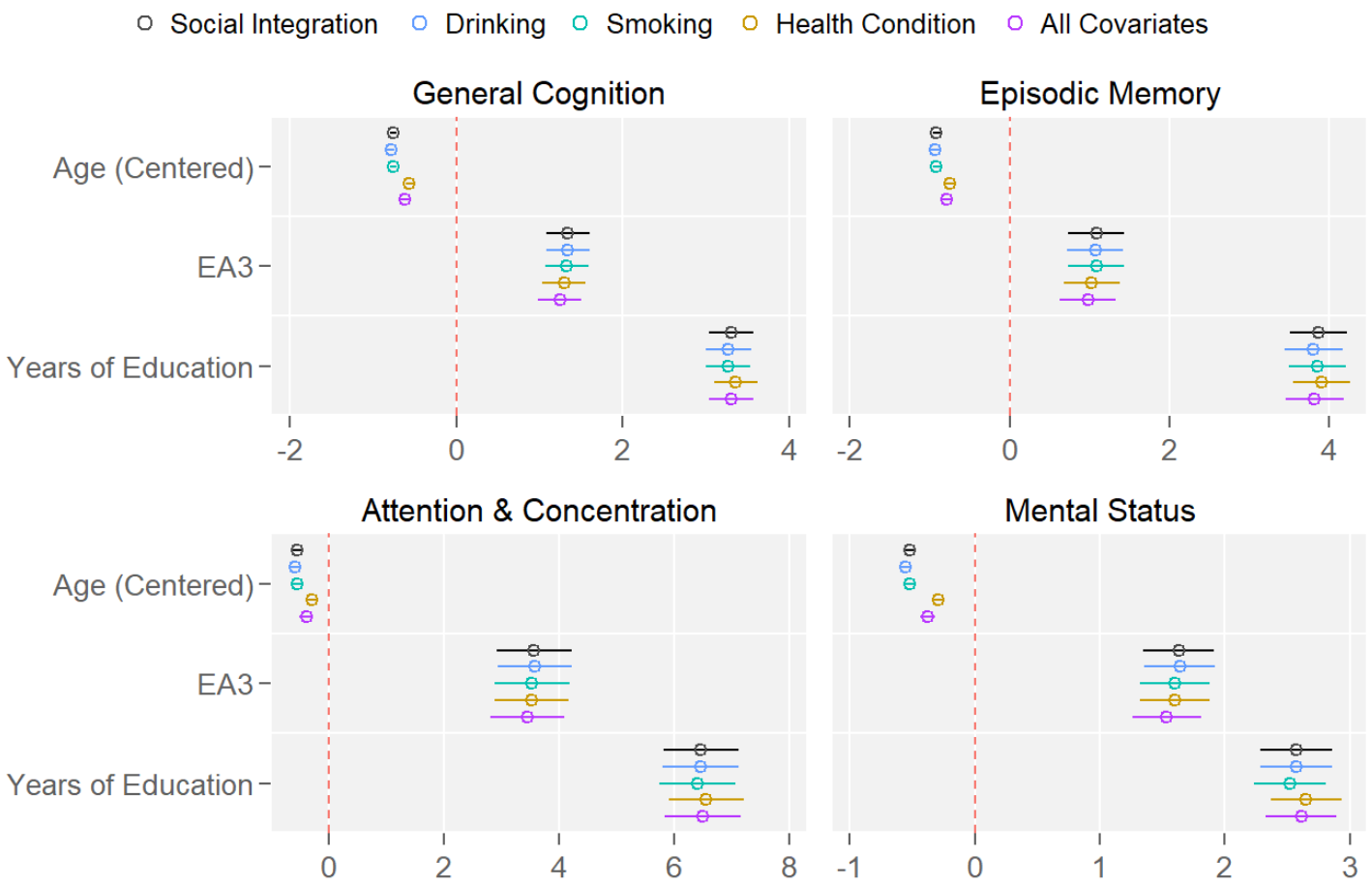


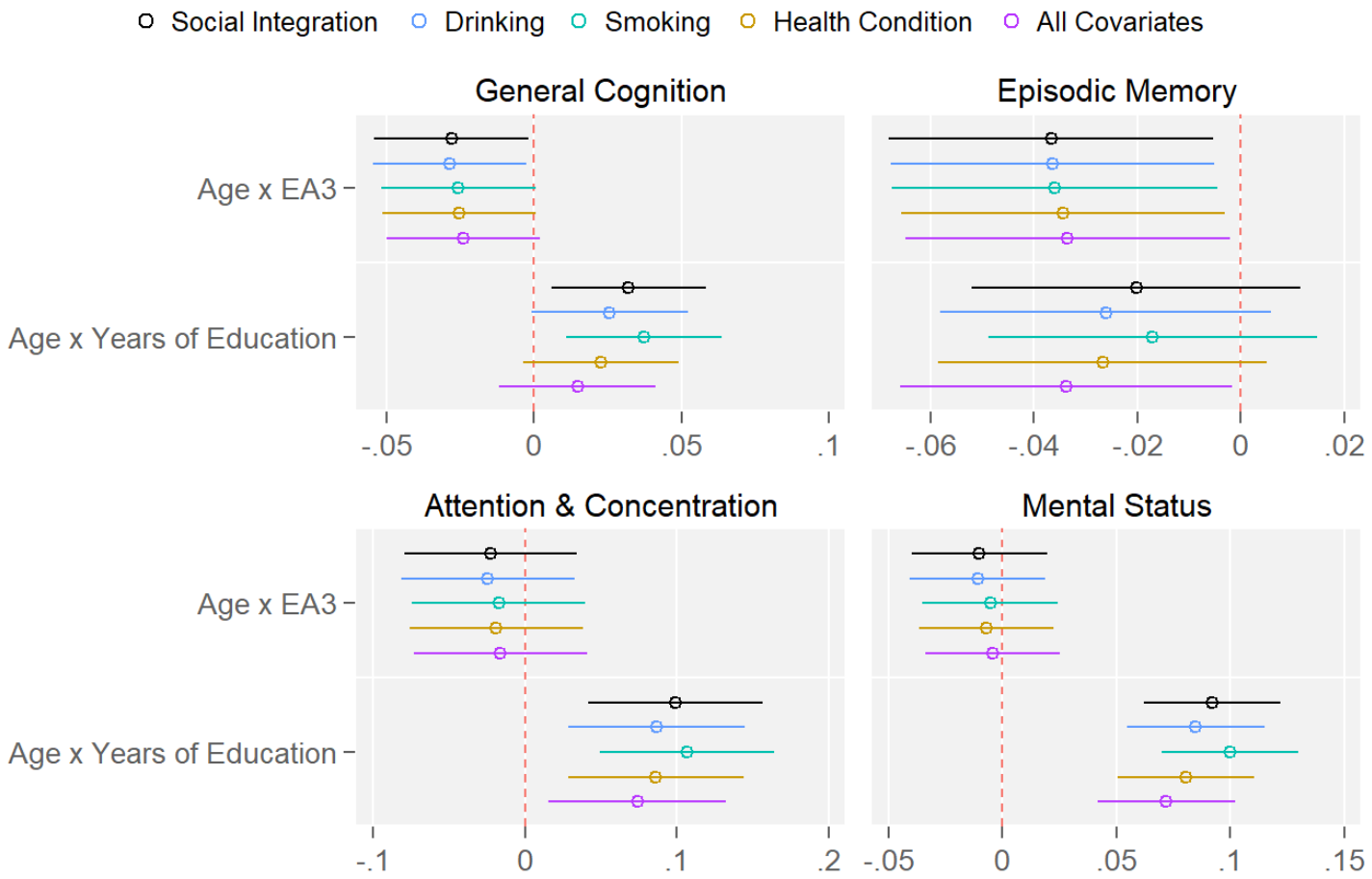
Figure 6. Intercept results from growth curve models on cognitive outcomes, with genetic risk score and years of education as predictors, controlling for covariates.



.

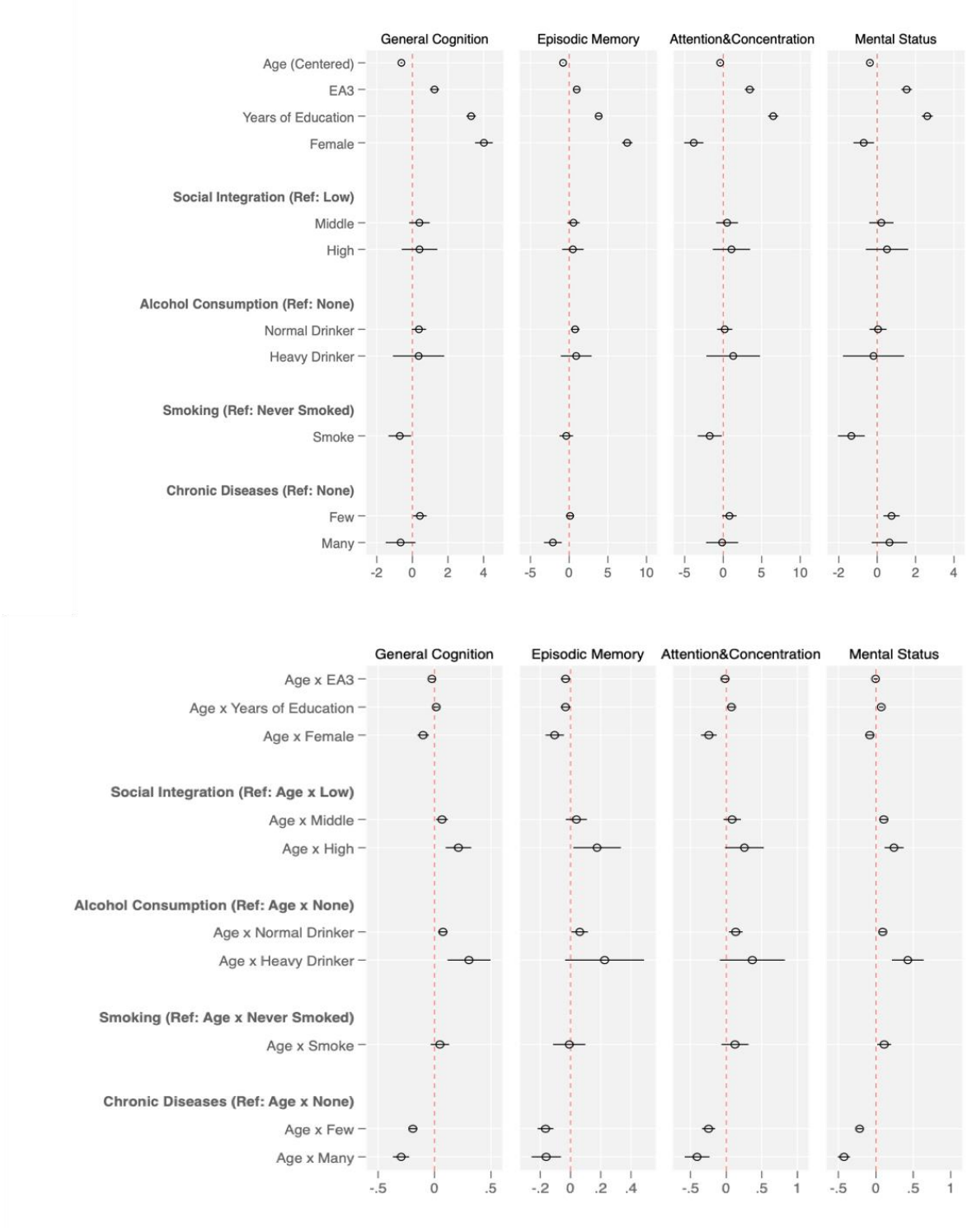
Note: EA3 and Years of education are standardised. Gender and 10 principal components are adjusted. 95% Confidence interval.

Figure 7. Slope results from growth curve models on cognitive outcomes, with genetic risk score and years of education as predictors, controlling for covariates.



Note: EA3 and Years of education are standardised. Gender and 10 principal components are adjusted. 95% Confidence interval.

Figure 8. Results of full growth curve models on cognitive outcomes.



Note: EA3 and Years of education are standardised. 10 principal components are adjusted. 95% Confidence interval.

Appendix 1. Linear regression models of EA3 on years of education and cognitive outcomes, no controls.

Variable	Years of Education	GC Wave 1	EM Wave 1	A&C Wave 1	MS Wave 1
EA3	0.31^{***}(0.12)	1.87^{***}(0.20)	1.52^{***}(0.22)	5.06^{***}(0.36)	2.10^{***}(0.19)
Observations	5,871	3,119	5,448	5,448	3,119
Adjusted R^2	0.095	0.027	0.008	0.034	0.036

Standard errors in parentheses, EA3 and years of education are standardised.
*** p<0.001, ** p<0.01, * p<0.05

Appendix 2. Mixed level linear regression on global cognition, without covariates.

Global Cognition			
	Edu	EA3	EA3 & Edu
Intercept	69.034***(0.195)	69.519***(0.204)	69.064***(0.194)
Age	-0.741***(0.020)	-0.763***(0.020)	-0.744***(0.020)
EA3		2.390***(0.135)	1.357*** (0.134)
EA3 X Age		-0.018 (0.013)	-0.028**(0.013)
Years of Education	3.731***(0.131)		3.295***(0.137)
Years of Education X Age	0.025* (0.013)		0.035** (0.013)
Female	4.056***(0.259)	3.557***(0.271)	4.052*** (0.257)
Female X Age	-0.108***(0.026)	-0.119***(0.026)	-0.107*** (0.026)
Var (Change)	0.34	0.35	0.34
Var (Initial)	58.34	67.64	56.86
Covariance	-1.33	-1.30	-1.30
Var (Residual)	61.83	61.48	61.82
AIC	251385.7	252091.4	251276.2
BIC	251554.6	252260.2	251461.8
Number. Individuals	5871	5871	5871
N	34203	34203	34203

Standard errors in parentheses
$^{\sim}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Years of education, EA3 score are standardized. 10 principal components are adjusted

Appendix 3. Mixed level linear regression on episodic memory, without covariates.

Episodic Memory			
	Edu	EA3	EA3 & Edu
Intercept	51.188*** (0.258)	51.735*** (0.268)	51.222***(0.258)
Age	-0.907***(0.024)	-0.933***(0.024)	-0.910***(0.024)
EA3		2.313***(0.177)	1.097*** (0.179)
EA3 X Age		-0.044*(0.016)	-0.037*(0.016)
Years of Education	4.222***(0.173)		3.868***(0.182)
Years of Education X Age	-0.031* (0.015)		-0.018 (0.016)
Female	7.510***(0.343)	6.922***(0.356)	7.507*** (0.342)
Female X Age	-0.110***(0.031)	-0.113***(0.031)	-0.109*** (0.031)
Var (Change)	0.30	0.30	0.30
Var (Initial)	94.59	107.67	93.61
Covariance	-2.15	-2.24	-2.11
Var (Residual)	130.58	130.33	130.56
AIC	273950.4	274529.3	273914.2
BIC	274119.2	274698.1	274099.9
Number. Individuals	5871	5871	5871
N	34203	34203	34203

Standard errors in parentheses

$^{\sim}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Years of education, EA3 score are standardized. 10 principal components are adjusted

Appendix 4. Mixed level linear regression on attention and concentration, without covariates.

Attention and Concentration			
	Edu	EA3	EA3 & Edu
Intercept	82.630*** (0.479)	83.515*** (0.488)	82.722***(0.474)
Age	-0.515***(0.043)	-0.549***(0.043)	-0.527***(0.043)
EA3		5.595***(0.323)	3.590*** (0.329)
EA3 X Age		0.007(0.028)	-0.023 (0.029)
Years of Education	7.614***(0.321)		6.464***(0.335)
Years of Education X Age	0.093* (0.028)		0.103*** (0.029)
Female	-3.782***(0.637)	-4.787***(0.650)	-3.785*** (0.630)
Female X Age	-0.256***(0.056)	-0.283***(0.057)	-0.254*** (0.056)
Var (Change)	0.88	0.92	0.88
Var (Initial)	348.95	375.82	338.19
Covariance	-1.96	-1.43	-1.93
Var (Residual)	397.38	396.65	397.21
AIC	313680.1	314096.6	313541.8
BIC	313848.9	3142654	313727.5
Number. Individuals	5871	5871	5871
N	34203	34203	34203

Standard errors in parentheses

~ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Years of education, EA3 score are standardized. 10 principal components are adjusted

Appendix 5. Mixed level linear regression on mental status, without covariates.

Mental Status			
	Edu	EA3	EA3 & Edu
Intercept	92.536*** (0.210)	92.924*** (0.214)	92.570***(0.208)
Age	-0.498***(0.022)	-0.514***(0.023)	-0.503***(0.022)
EA3		2.448***(0.141)	1.647*** (0.144)
EA3 X Age		0.019(0.015)	-0.010*(0.015)
Years of Education	3.092***(0.141)		2.565***(0.147)
Years of Education X Age	0.092*** (0.015)		0.096*** (0.015)
Female	-0.645*(0.279)	-1.037***(0.248)	-0.647* (0.276)
Female X Age	-0.091**(0.029)	-0.112***(0.030)	-0.090** (0.029)
Var (Change)	0.45	0.48	0.45
Var (Initial)	64.55	69.47	62.38
Covariance	-1.15	-1.05	-1.14
Var (Residual)	77.78	77.38	77.75
AIC	259129.6	259527.7	258975.3
BIC	259298.4	259696.5	259160.9
Number. Individuals	5871	5871	5871
N	34203	34203	34203

Standard errors in parentheses
~ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Years of education, EA3 score are standardized. 10 principal components are adjusted.

Note: Figure 2-5 are based on Appendix 2-5

Appendix 6. Mixed level linear regression on global cognition, with covariates.

	Social Integration	Drinking	Smoking	Health Condition	All Covariates
Intercept	68.977***(0.199)	68.903***(0.214)	69.195***(0.197)	68.646***(0.220)	68.512***(0.249)
Age	-0.757***(0.020)	-0.782***(0.021)	-0.757***(0.020)	-0.558***(0.023)	-0.616***(0.026)
EA3	1.341***(0.134)	1.341*** (0.134)	1.330*** (0.134)	1.293***(0.132)	1.244$^{~}$(0.132)
EA3 X Age	-0.028*(0.013)	-0.029*(0.013)	-0.026$^{~}$(0.013)	-0.026$^{~}$ (0.013)	-0.024(0.013)
Years of Education	3.297***(0.136)	3.269***(0.137)	3.267***(0.137)	3.356***(0.135)	3.302***(0.136)
Years of Education X Age	0.032* (0.013)	0.026$^{~}$ (0.014)	0.037** (0.013)	0.023$^{~}$ (0.013)	0.015(0.014)
Female	4.036***(0.256)	4.095*** (0.259)	4.037*** (0.257)	3.989*** (0.253)	5.021***(0.255)
Female X Age	-0.104***(0.026)	-0.092*** (0.026)	-0.105*** (0.026)	-0.117***(0.026)	-0.102***(0.026)
Social Integration					
Middle	0.387(0.298)				0.397(0.295)
High	0.254(0.514)				0.401(0.510)
Middle X Age	0.076**(0.027)				0.066*(0.026)
High X Age	0.244***(0.058)				0.212***(0.058)
Drinking					
Normal Drinker		0.325(0.207)			0.371$^{~}$(0.205)
Heavy Drinker		0.039(0.738)			0.353(0.734)
Normal X Age		0.092***(0.020)			0.074***(0.021)
Heavy X Age		0.363***(0.097)			0.305**(0.097)
Smoking					
Smoke Ever			-1.003**(0.329)		-0.706*(0.326)
Smoke X Age			0.108*(0.042)		0.048(0.042)
Health Conditions					
Few				0.500* (0.194)	0.425*(0.195)
Many				-0.563(0.427)	-0.659(0.427)
Few X Age				-0.206***(0.020)	-0.193***(0.020)
Many X Age				-0.321***(0.037)	-0.296***(0.037)

Appendix 6. Mixed level linear regression on global cognition, with covariates. (Continued.)

Var (Change)	0.33	0.33	0.33	0.33	0.32
Var (Initial)	56.42	56.60	56.51	54.20	53.54
Covariance	-1.27	-1.29	-1.27	-1.14	-1.12
Var (Residual)	61.78	61.79	61.82	61.65	61.62
AIC	251236.4	251212.1	251262.5	251031.9	250964.8
BIC	251454.9	251431.6	251465.1	251251.3	251268.6
Number. Individuals	5871	5871	5871	5871	5871
N	34203	34203	34203	34203	34203

Standard errors in parentheses

$^{\sim}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Years of education, EA3 score are standardized. 10 principal components are adjusted.

Appendix 7. Mixed level linear regression on episodic memory, with covariates.

	Social Integration	Drinking	Smoking	Health Condition	All Covariates
Intercept	51.12***(0.265)	50.855***(0.287)	51.292***(0.263)	51.142***(0.296)	50.745***(0.337)
Age	-0.918***(0.024)	-0.937***(0.026)	-0.915***(0.024)	-0.750***(0.029)	-0.788***(0.033)
EA3	1.082***(0.178)	1.069***(0.178)	1.083*** (0.179)	1.025***(0.177)	0.976*(0.178)
EA3 X Age	-0.0367*(0.016)	-0.036* (0.016)	-0.036*(0.016)	-0.034* (0.016)	-0.034*(0.016)
Years of Education	3.864***(0.182)	3.802***(0.184)	3.850***(0.182)	3.901***(0.181)	3.816***(0.183)
Years of Education X Age	-0.020 (0.016)	-0.026(0.016)	-0.017 (0.016)	-0.027$^{\sim}$ (0.016)	-0.034*(0.016)
Female	7.493***(0.342)	7.618***(0.345)	7.499*** (0.342)	7.403*** (0.339)	7.503***(0.343)
Female X Age	-0.107**(0.031)	-0.099*(0.031)	-0.108** (0.031)	-0.117***(0.031)	-0.106**(0.031)
Social Integration					
Middle	0.567(0.410)				0.559(0.407)
High	0.387(0.710)				0.481(0.708)
Middle X Age	0.045(0.035)				0.038(0.035)
High X Age	0.202*(0.080)				0.175*(0.080)
Drinking					
Normal Drinker		0.780**(0.287)			0.769**(0.286)
Heavy Drinker		0.262*(0.133)			0.906(1.014)
Normal X Age		0.073**(0.028)			0.060*(0.028)
Heavy X Age		0.262*(0.133)			0.225$^{\sim}$(0.133)
Smoking					
Smoke Ever			-0.572(0.447)		-0.370(0.447)
Smoke X Age			0.039(0.054)		-0.009(0.054)
Health Conditions					
Few				0.154* (0.267)	0.117(0.269)
Many				-2.100***(0.587)	-2.108***(0.588)
Few X Age				-0.175***(0.026)	-0.166***(0.027)
Many X Age				-0.179***(0.049)	-0.162**(0.050)

Appendix 7. Mixed level linear regression on episodic memory, with covariates. (Continued.)

Var (Change)	0.30	0.29	0.30	0.29	0.29
Var (Initial)	93.32	93.17	93.48	91.15	90.59
Covariance	-2.10	-2.11	-2.10	-2.01	-2.01
Var (Residual)	130.53	130.55	130.572	130.368	130.34
AIC	273901.9	273871.9	273908	273792.6	273744
BIC	274121.4	274091.3	274110.6	274012	274047.8
Number. Individuals	5871	5871	5871	5871	5871
N	34203	34203	34203	34203	34203

Standard errors in parentheses

$^{\sim}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Years of education, EA3 score are standardized. 10 principal components are adjusted.

Appendix 8. Mixed level linear regression on attention and concentration, with covariates.

	Social Integration	Drinking	Smoking	Health Condition	All Covariates
Intercept	82.594*** (0.487)	82.627*** (0.524)	82.999*** (0.483)	82.061*** (0.540)	82.107*** (0.611)
Age	-0.541*** (0.044)	-0.591*** (0.047)	-0.552*** (0.044)	-0.291*** (0.053)	-0.389*** (0.059)
EA3	3.566*** (0.329)	3.582*** (0.329)	3.528*** (0.329)	3.525*** (0.328)	3.446*** (0.329)
EA3 X Age	-0.023(0.029)	-0.024(0.029)	-0.017(0.029)	-0.019(0.029)	-0.016(0.029)
Years of Education	6.466***(0.335)	6.461***(0.338)	6.404***(0.335)	6.554***(0.336)	6.487***(0.338)
Years of Education X Age	0.099**(0.029)	0.087**(0.030)	0.107***(0.029)	0.086**(0.029)	0.074*(0.030)
Female	-3.803***(0.629)	-3.750***(0.635)	-3.812***(0.629)	-3.844***(0.629)	-3.819***(0.633)
Female X Age	-0.251***(0.056)	-0.232***(0.056)	-0.250***(0.056)	-0.266***(0.056)	-0.243***(0.057)
Social Integration					
Middle	0.507(0.726)				0.506(0.724)
High	0.885(1.240)				1.072(1.238)
Middle X Age	0.095(0.063)				0.083(0.063)
High X Age	0.304*(0.140)				0.256~(0.140)
Drinking					
Normal Drinker		0.119(0.505)			0.196(0.505)
Heavy Drinker		0.710(1.777)			1.297(1.776)
Normal X Age		0.158**(0.048)			0.133**(0.049)
Heavy X Age		0.467*(0.232)			0.367(0.232)
Smoking					
Smoke Ever			-2.195**(0.792)		-1.751*(0.795)
Smoke X Age			0.210*(0.097)		-0.123(0.097)
Health Conditions					
Few				0.962*(0.475)	0.810~(0.478)
Many				0.052(1.061)	-0.136(1.063)
Few X Age				-0.271***(0.047)	-0.247***(0.047)
Many X Age				-0.452**(0.088)	-0.410**(0.088)

Appendix 8. Mixed level linear regression on attention and concentration, with covariates. (Continued.)

Var (Change)	0.87	0.88	0.88	0.87	0.86
Var (Initial)	338.23	337.92	337.00	334.6	332.81
Covariance	-1.86	-1.94	-1.86	-1.70	-1.64
Var (Residual)	397.27	397.08	397.23	396.71	396.70
AIC	313636.2	313524.9	313528.5	313477.6	313452.2
BIC	313754.7	313744.3	313731.1	313697	313756.0
Number. Individuals	5871	5871	5871	5871	5871
N	34203	34203	34203	34203	34203

Standard errors in parentheses
$^{\sim}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Years of education, EA3 score are standardized. 10 principal components are adjusted.

Appendix 9. Mixed level linear regression on mental status, with covariates.

	Social Integration	Drinking	Smoking	Health Condition	All Covariates
Intercept	92.50*** (0.213)	92.59*** (0.231)	92.78*** (0.212)	91.863*** (0.238)	92.007*** (0.270)
Age	-0.520*** (0.023)	-0.554*** (0.024)	-0.524*** (0.023)	-0.295*** (0.027)	-0.379*** (0.029)
EA3	1.629*** (0.143)	1.640*** (0.144)	1.599*** (0.144)	1.596*** (0.142)	1.535*** (0.142)
EA3 X Age	-0.010 (0.015)	-0.011 (0.015)	-0.005 (0.015)	-0.007(0.015)	-0.004 (0.015)
Years of Education	2.572*** (0.146)	2.572*** (0.148)	2.518*** (0.147)	2.648***(0.145)	2.610*** (0.150)
Years of Education X Age	0.092*** (0.015)	0.085*** (0.015)	0.100*** (0.015)	0.081***(0.015)	0.072*** (0.015)
Female	-0.664* (0.275)	-0.667* (0.278)	-0.671* (0.275)	-0.670*(0.272)	-0.701* (0.273)
Female X Age	-0.087** (0.029)	-0.070* (0.030)	-0.086** (0.029)	-0.102***(0.029)	-0.081** (0.029)
Social Integration					
Middle	0.210 (0.326)				0.218 (0.322)
High	0.339 (0.568)				0.511 (0.562)
Middle X Age	0.117*** (0.030)				0.105*** (0.029)
High X Age	0.282*** (0.065)				0.242*** (0.065)
Drinking					
Normal Drinker		-0.045 (0.229)			0.045 (0.226)
Heavy Drinker		-0.702 (0.820)			-0.192 (0.813)
Normal X Age		0.114***(0.023)			0.091***(0.023)
Heavy X Age		0.511*** (0.109)			0.427*** (0.109)
Smoking					
Smoke Ever			-1.743***(0.359)		-1.345*** (0.356)
Smoke X Age			0.185***(0.047)		0.111*(0.047)
Health Conditions					
Few				0.872***(0.215)	0.746** (0.315)
Many				0.816˜(0.473)	0.641(0.473)
Few X Age				-0.236***(0.022)	-0.218***(0.022)
Many X Age				-0.462**(0.041)	-0.427***(0.041)

Appendix 9. Mixed level linear regression on mental status, with covariates. (Continued.)

Var (Change)	0.44	0.44	0.44	0.44	0.43
Var (Initial)	61.75	62.21	61.68	59.56	58.58
Covariance	-1.10	-1.13	-1.09	-0.92	-0.86
Var (Residual)	77.73	77.68	77.77	77.44	77.38
AIC	258926.8	258922.4	258945.7	258730.1	258635.3
BIC	259146.2	269141.9	259148.3	258949.5	258939.1
Number. Individuals	5871	5871	5871	5871	5871
N	34203	34203	34203	34203	34203

Standard errors in parentheses
$^{\sim}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Years of education, EA3 score are standardized. 10 principal components are adjusted.

Note: Figure 6-8 are based on results from Appendix 6-9.