Genes related to education and frailty among older adults in the United States

Brooke Huibregste

Breanne L. Newell-Stamper

Jason D. Boardman

University of Colorado

Note: This paper uses data from the Health and Retirement Study (HRS). The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. Genotyping funds for this project were provided by National Institute of Health's (NIH) Director's Opportunity for Research awards using American Reinvestment and Recovery Act funds (RC2 AG036495-01, RC4 AG039029-01). Support was also provided by a NIA training grant (T32AG052371).

Abstract

Using data from a sample of 5,344 non-Hispanic and white adults from the Health and Retirement Study (HRS), we expand on research that links education and frailty among older adults by considering the role of genes associated with education. We calculate a genome-wide polygenic score (PGS) for education and demonstrate a strong and negative association between genes associated with education and symptoms of frailty in later life using two different indicators of frailty (Deficit accumulation and the Paulson-Lichtenberg frailty index). We also show that this association exists above and beyond years of completed education and we demonstrate that this association becomes weaker as older adults approach their 80s. Our results contribute to the education-health literature and suggest new and important pathways through which years of education may be linked to successful aging.

Introduction

One of the most important areas of research for demographers involves the characterization of health and the determinants of health of aging populations (Christensen et al. 2009). One particular area that has grown over the past 25 years is research that consistently demonstrates a robust relationship between education and health (Link and Phelan 1995). The protective effect of increasing years of education is evident across a number of morbidities and is fairly consistent across different sociodemographic groups in the US (Zajacova and Lawrence 2018). In this paper, we focus on a critical aging-related phenotype, *frailty*, and evaluate the extent to which this indicator of overall health among the elderly is linked to years of education. Previous work has shown educational gradients in frailty at both the population (Etman et al, 2012, Theou et al., 2013) and individual levels (Crimmins et al, 2010, Szanton et al, 2010) but no existing work has evaluated the hypothesis that some of this association is due to genetic influences that affect education and subsequently frailly.

The purpose of the study is to explore the possibility that genetic loci that are associated with educational attainment are also implicated in the reduced likelihood of frailty in later life (60+ years). Importantly, we evaluate the possibility that genes related to education also predict frailty above and beyond the effect of educational attainment. While there is preliminary evidence that the PGS_{educ} has lasting benefits through the life course, we seek to explore how these effects manifest over biological age. That is, is the potential effect of the PGS_{educ} most predictive of frailty more or less important as individual ages? Such answers will help to elucidate the relationship effects of education on frailty by exploring the genetic mechanisms underpinning both measures.

Genetics and Years of Completed Education

A recent meta-analysis of twin and family studies show that up to 40% of variance in educational attainment can be explained by genetic factors (Brainigan, McCallum & Freese, 2013).

Using genetic markers, it is now possible to quantify an individual's genetic propensity for high levels of educational attainment. One increasingly popular method is the polygenic score (PGS) approach (Dudbridge 2013), which has led to a number of advances over the past two decades in predicting disease (Jostins & Barret, 2011). Such successes are reflective of a growing consensus that complex phenotypes, such as educational attainment, are influenced by many genetic loci with very small effect sizes (i.e., highly polygenic, Vissher et al., 2017). The PGS for educational attainment (PGS_{educ}) is a single score representing genome wide influence on academic success, as measured by formal years of schooling. Initially, social scientists developed this score (Reitvelt et al., 2013, Okbay et al., 2016, Lee et al., 2018) to explain variation in schooling due to genetic factors and the current score explains roughly 10% of the variance in education (Lee et al. 2018). In early and midlife, the PGS_{educ} is predictive of other measures of academic success and cognitive performance (e.g., general cognitive ability, standardized exam scores, highest math course completed; Lee et al., 2018, Belsky et al., 2018). Into adulthood, the PGS_{educ} predicts social mobility and indicators of economic success (e.g., occupational status, asset accumulation, financial stability, and wealth at retirement; Belsky et al., 2016, Belsky et al., 2018, Barth, Papageorge, and Thom, 2018).

While there is evidence that genes associated with educational attainment predict indicators of success, the relationship with indicators of *health* is less established but is growing. That is, do *genes* associated with educational attainment also predict health outcomes? Results from large consortia suggest significant genetic overlap between genes for educational attainment and a range of health indicators (e.g., Alzheimer's disease, ischemic stroke, psychiatric conditions, vascular-metabolic diseases, smoking status, and other physiological measures such as body-mass index; Bulik-Sullivan et al., 2015, Hagenaars et al., 2016, Gandal et al., 2018, Anttila et al., 2018). Indirect evidence for this association comes from two additional studies. First, Marioni et al. (2016) found that a child's PGS_{educ} was predictive of mortality, as measured by the paternal and maternal lifespan

(Marioni et al., 2016). Second, Boardman et al. (2015) provide evidence for genetic correlation (rG) for genes linked to years of education and genes linked to self-rated health.

Aging, genes, and frailty

From a medical perspective, frailty is a state of reduced physiological resilience and increased vulnerability to adverse events. Patients who are frail are more likely to be hospitalized, lose daily independence, have negative outcomes with medical procedures (e.g., poor response to surgeries), and have increased risk of death (Mitnitski, Mogilner, and Rockwood. 2001; Fried et al., 2001; Hamaker et al., 2012; Jung et al., 2014; Mitnitski et al. 2015; Rodriguez-Manas and Fried 2015; Hanlon et al., 2018). Frailty is an indicator of general health predicts morbidity and mortality and is considered an indicator of biological age (Fried et al. 2001; Sanderson and Scherbov, 2014; Mitnitski et al., 2017). As demographic shifts in population age-structure occur worldwide, the result is a growing population at risk for frailty, which is a debilitating and financially costly age-related syndrome (Morley et al., 2013; Goldman et al., 2013). As such, it is imperative to understand the predictors and mechanisms governing who is most at risk for frailty.

Though aging is the greatest known risk factor for frailty (Rockwood and Mitnitski, 2011), not all aging individuals become frail, and individuals develop frailty at different rates (Mitnitski & Rockwood, 2016). Those with lower levels of education are far more likely than those with relatively high levels of education to evidence symptoms of frailty at an early age (Santos-Eggimann et al. 2009). There are two competing hypotheses regarding effects of education across the life course which may explain the related gradients for frailty. The *cumulative advantage* hypothesis posits that educational gradients should increase with age (O'Rand, 2006). Alternatively, the alternative, *age as a leveler* hypothesis suggests these differences are diminished later in life (Preston, Hill, & Drevensted, 1988). To date, there is evidence for both perspectives depending on the specific measure of frailty, the age composition of the study, and whether or not frailty is measured as a static indicator of

current health or a within person measure of change in indicators of frailty over time (Yang and Lee 2010).

Bringing measured genetic polymorphisms to bear may shed light on the relevance of these two age-related models. Previous research has shown that roughly 20-40% of frailty is genetically oriented (Sanders et al. 2016; Young et al. 2016). In an oversimplification of this very complex process consider the possibility that two individuals with otherwise identical states of frailty may have arrived to this state via very different paths: one because of their environmental exposures across their lifetime and the other simply because of their genetic composition. Thus, environmentally oriented frailty and genetically oriented frailty should be considered somewhat different morbidities despite their identical appearance in terms of measurement and assessment. One way to evaluate the relevance of the two age-related models discussed above is to consider changes in the effect of the PGSed with increasing ages. If the effect of PGSed on frailty is the same across ages among adults over the age of 60 then it provides some indirect support for the cumulative advantage perspective and it suggests that some of these cumulative advantage may have origins in genes linked to educational success. On the other hand, if the effect of the educational PGS on frailty decreases with increasing age then it provides some support for the age as a leveler perspective and importantly it stresses that age even levels the playing field with respect to genetic influence on the educational determinants of frailty.

Material and Methods

[Table 1 about here]

Data

The data comes from the Health and Retirement Study (HRS), a biannual panel study tracking physical, emotional, and economic wellbeing during the transition into older age (Juster & Suzman, 1995, Sonnega et al., 2014). These respondents were born between 1900 and 1970 with the

interquartile range (IQR) of birth years spanning from 1930 to 1950. The HRS is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan. This study focuses on a sample of 5,344 HRS respondents with genotype data collected between 2006-2008 and that had data for both frailty measures. Descriptive statistics for all variables are provided in Table 1. Because of complications due to population stratification and the use of the PGS_{educ} values across socially identified racial and ethnic groups, our analyses are limited to those who identify as non-Hispanic and white. Descriptive statistics for all variables used in the HRS are presented in Table 1.

PGS_{educ}

Genotypes were assessed using the llumina HumanOmni2.5 BeadChips, with coverage of over 2.4 million genetic loci (i.e., single nucleotide polymorphisms [SNPS]). Standard quality control procedures were conducted (Ware et al., 2018). The PGS_{educ} was calculated using the sample excluding participants from the Social Science Genetic Association Consortium (SSGAC; Okbay et al., 2016). Scores were standardized within the sample.

Frailty indices

Two metrics of frailty were used to assess five waves of the HRS (2004-2012). These waves were selected due to consistency in item measurement, and have also been used in previous research on frailty (Mezuk et al., 2016). When possible, items were pulled from a harmonized longitudinal file prepared by the RAND Center on the Study of Aging (RAND, 2014). When unavailable in the RAND file, matching items were identified in the biannual files. For both metrics of frailty, scores are treated as both continuous and categorical. Continuous measures reflect an unweighted count of the number of health problems (i.e., symptoms, signs, functional impairments, or abnormal

laboratory values), which are collectively referred to as "deficits." Counting deficits stratifies respondents based on their level of functional decline, and thus, their degrees of vulnerability (Rockwood et al., 2005). Categorical measures were treated as binary and are based on clinical cutoff that have emerged to classify an individual's *frailty status* (i.e., frail or non-frail). Importantly, frail individuals have increased mortality compared to individuals of the same age (Vaulpel, Manton, & Stallard, 1979).While frailty is considered a reversible or dynamic state transitioning back from frailty is not common (Gill et al. 2006). The explanation for this is that once enough homeostatic reserve is lost it cannot be regained.

Paulson-Lichtenberg frailty index (PLFI)

As described by Paulson and Lichtenberg (2015), the frailty phenotype was designed to be a best-fit representation of the Fried et al. 2001 frailty phenotype using HRS data. The PLFI included five symptoms: wasting (i.e., individual reported loss of at least 10% of body weight over a 2-year period), weakness (i.e., "Because of health problems, do you have any difficulty with lifting or carrying weights over 10 pounds, like a heavy bag of groceries"), slowness (i.e., "Because of a health problem, do you have any difficulty with getting up from a chair after sitting for long periods), fatigue (i.e., "Have you had any of the following persistent or troublesome problems: sever fatigue or exhaustion?"), and falls ("Have you fallen down in the past 2 years"). The continuous PLFI measure had a range of 0-5, whereas the binary measure of frailty status used the established cut off of PLFI >3 as indicative of "frail" (Paulson & Lichtenberg, 2015).

Deficit accumulation model frailty index (FI)

Frailty in the HRS was also operationalized using the deficit accumulation model put forth by Rockwell et al. 2005, and Mitniski, Song, and Rockwood, 2013. The FI is a calculated ratio of health

deficits out of the total number of possible deficits (e.g., 10 deficits present / 30 possible deficits indicates a FI of 0.33). The FI developed for use in the HRS uses 30 self-report health measures and was recreated using the item list published in Mezuk et al., 2016. Items included a variety of deficits such as difficulties with activities of daily living (e.g., dressing, bathing, toileting, cooing, shopping, changes activities of daily living), problems with pain (e.g., general pain, back pain, headache), problems with worsening memory or dementia, disturbances in sleep (e.g., persistent fatigue, problems falling or staying asleep), motor impairment (e.g., falling, impaired mobility, gross-motor impairment, fine motor impairment), and presence of health conditions (e.g., incontinence, cancer, arthritis, psychiatric conditions, depression, lung disease, respiratory problems, diabetes, stroke, angina, heart failure, heart attack, or high blood pressure). The continuous FI is a proportion ranging from 0-1, while the established cutoff of FI>0.25 defines frailty status (Rockwell et al. 2005).

Statistical analysis

Statistical analyses were conducted using R (version 3.4.1, Project for Statistical Computing; R Core Team, 2015) and Stata (StataCorp, 2011). Simple association of frailty score with polygenic score was done by chi-squared test of independence. Because frailty was repeatedly assessed we use all data across waves. In total we had 827 individuals with one observation, 1186 with two, 3330 with three, and 1 person had four frailty observations. Multi-level regression with the *xtmixed* procedure in Stata was used to model the association of PGS_{educ} and frailty score in which observations are nested within people. We report the intra class correlation coefficient (ICC) for each model. Similarly, multi-level logistic regression was used with the *xtmelogit* command in Stata to model PGS_{educ} and frailty status (frail / non-frail). Level 1 error variance was assumed to be $\frac{\pi^2}{3}$ (Guo and Zhao 2000). All models control for the top five principle components (PCs) to control for effects of population

stratification or spurious association due non-causal allele frequency differences across ancestry groups (Patterson, Price, & Reich, 2006).

Results

[Table 2 about here]

Table 2 presents bivariate associations between PGS_{educ} (cut into quartiles) and the four metrics of frailty. These results provide the first evidence for our hypothesis linking genes related to educational outcomes and the indicators of frailty among older adults. The PLFI is the highest among those in the 1st quartile (lowest level) of the education PGS_{educ} ($\bar{x}$ = 1.29) and the least frail are those in the 4th quartile of the PLFI ($\bar{x}$ = 1.18). This difference is a small effect size (d = .09) but it remains statistically and substantively significant (the p-value for this test is derived from a one-way ANOVA test and demonstrates that this relationship is statistically significant (p<.001). We show comparable estimates using the FI, a more comprehensive measure of frailty in which again, those with the lowest education PGS_{educ} have a frailty score ($\bar{x}$ = 24.41) that is significantly higher than the frailty score among those with the highest education PGS_{educ} ($\bar{x}$ = 23.07). As with the PLFI, the effect size remains quite small (d = .11) but important nevertheless. Table 2 also evaluates the same associations but at their respective thresholds to identify a state of frailty. While only 14.68% of those with the highest education PGS_{educ} were in a frail state according to the PL score 17.08% of those with the lowest education PGS_{educ} scores were in a frail PLFI state and this same association is seen with the threshold for the frailty index. Specifically, while 40.27% of those with low education PGS_{educ} were frail at the time of the interview, only 36.72% of those with high education PGS_{educ} scores were frail. As with the continuous indicators, both binary assessments of frailty status were statistically significant (pr. < .025 and < .008, respectively).

[Table 3 about here]

Table 3 presents the results from multilevel analyses for the two continuous indicators of frailty described above in which observations are nested within individuals. For each measure we present the results of three models. The first regresses the frailty score on the education PGS_{educ} with controls for gender, age, and the top 5 PCs. The second introduces a control for years of education and the third introduces the interaction between the PGS_{educ} and age to evaluate the possibility of age related changes in the influence of the PGS_{educ} on frailty. Model 1 provides a baseline indicator for the effect of the education PGS_{educ} on PLFI. The effect (b = -.06) suggests that a one standard deviation increase in the education PGS_{educ} reduces frailty by .06 points. As with the bivariate associations this denotes a small effect size (d = .05) but again it remains a statistically significant and meaningful association. Model 2 introduces years of completed education as a mediating mechanism to link education PGS_{educ} to frailty. As expected, the PGS_{educ} coefficient is significantly reduced (b = -.03) but most importantly, the association remains statistically significant. This provides evidence for our primary hypothesis. Namely, that genes linked to educational attainment provide health protections that are *above and beyond* each additional year of formal education. Model 3 evaluates our interest in this association as individual's age. Accordingly, we introduce an interaction between age and the education PGS_{educ}. As shown in Model 3, the interaction is positive and significant which suggests that the protective effects of the education PGS_{educ} on frailty diminish with age. To better gauge the meaning of this interaction, we used the postestimation *margins* command in Stata to retrieve parameter estimates and confidence intervals for age specific slopes for the education PGS_{educ} - Frailty association. These estimates are shown graphically in Figure 1a. The horizontal line represents the null hypothesis that there is no association between education PGS_{educ} and frailty. We show the largest effects (b = - .06) among those who are 65 years old, the average effect (b = - .03) among those who are 75, and non-significant associations among those who are 80 and 85.

[Figure 1 about here]

A very similar story is shown in Models 4-6 in which the dependent variable is now the deficits accumulation model or FI. Here, the baseline association (b = -.84) is evident above and beyond controls for age, gender, and the five principal components and this effect is nearly cut in half after controlling for years of education in Model 5 (b = - .44). As with the PLFI, this association remains statistically significant despite controlling for education. Similarly, the association is reduced as people age as indicated by the positive interaction in Model 6 (b = .24) which is statistically significant. The functional form of this interaction and the age thresholds at which education PGS_{educ} is linked to frailty is nearly identical to the PL score despite using different and more comprehensive indicators of frailty.

The results presented in Table 4 replicate the models in Table 3 but use a binary indicator of a frailty status with an a priori threshold for each measure described above. As with the continuous indices, the education PGS_{educ} is significantly associated with reduced likelihood of frailty using the established cutoffs for the PLFI (b = -.16) and the FI (b= -.21). Statistical controls for years of completed education reduce these associations by more than one-half for both PLFI (b=-.07) and FI (b = -. 09) and rendering the main effect for the PLFI to drop below statistical significance (95% CI [-.16, .03]). As with the continuous indicators, the interaction with age is both positive and statistically significant. Figures 1c and 1d plot the fitted probability of each respective indicator of frail status as a function of age and education PGS_{educ} in which the solid line is among those with the lowest education PGS_{educ} (-2SD) and the dashed line is among those with the highest education PGS_{educ} (+2SD). In both cases, the story is nearly identical to the continuous indicators in which the effect is the most evident among those ages 75 and younger and non-existent among those 80 and older.

Discussion

A breadth of work has established a link between educational attainment and health (Zajakova and Lawrence 2018). Recently, attention has been directed at extending this research to study the link between educational attainment and an age-related health outcome, frailty. To the best of our knowledge, this is the first study to explore whether *genes* related to educational attainment directly or indirectly influence health and aging, as measured by frailty. Specifically, we hypothesized that the PGS_{educ} would be predictive of frailty, and this association would exists above and beyond the direct effects of actual educational attainment. That is, if the genetic mechanisms are dependent on education then we would expect that the association of the PGSscore would be rendered non-significant when controlling for education in the model. Alternatively, if the genetic mechanisms are influencing health above and beyond years of education then we should continue to see a significant association between PGSeduc. Indeed, that is what we observed. Across two frailty metrics we found that genes related to educational attainment predict frailty. That is, participants with higher PGS_{educ} scores had better general health (i.e., less functional decline) compared to participants with lower scores. This held true for both a comprehensive frailty index (FI) and the measure reflecting the frailty phenotype described by Fried (2002; PLFI). Similarly, participants with higher PGS_{educ} were less likely to be classified as "frail" based on established cut-offs. Standing alone, this finding may not be entirely surprising. As the PGS_{educ} is predictive of actual educational attainment, it is possible that that the genetic effects operate indirectly through exposure to education. Thus, we explored an alternative explanation in which the PGS_{educ} operates independently of actual educational attainment.

While we did not explore other intermediate phenotypes between the PGS_{educ} and frailty, several biological, cognitive, social, or psychosocial mediators have been put forth linking education to health. The bulk of these involve benefits derived from years of completed education. Accordingly, the residual effect of PGSeduc and frailty suggests that there is something critical in the

education-health process that also operates above and beyond years of completed education. In their comprehensive review Zajakova and Lawrence (2018: 275) discuss what they call a "signaling or credentialing perspective" in which the attainment of specific degrees provides new sources of human and social capital that frames an individual as productive or skilled. Accordingly, it may be that individuals with higher PGSed scores present themselves in a manner that is concordant with a successful or productive individual and thus create a response from others in which these signals lead to a positive framing of an individual that exists above and beyond their years of education. This is what is referred to as an evocative gene-environment correlation because an individual's cumulative genotype may evoke environments that are associated with both increasing education and reduced risks of frailty. This perspective is in line with our findings but our analyses cannot rule out other explanations.

Other explanations include but are not limited to the following. The education PGS could be predicting health which then influences years of education. There is a large and growing body of work characterizing the rate of biological aging differences across social groups with a focus on education (Sanderson and Scherbov 2014; Mintinski, Howelett, and Rockwood 2017) and it is possible that those with higher education PGS scores are simply aging at a slower rate that those with lower PGS scores. A critical psychological mechanism could be the role of self-efficacy or mastery in which individuals with higher educational PGS may also have higher levels of efficacy that lead to both educational success, increased resilience, and delayed frailty onset (Stretton et al. 2006). This same perspective is supported by work linking education to hopelessness and other indicators of sense of control (Mitchell et al. 2016). It is possible that the education PGS is involved in complex biological and psychiatric processes that reduce the sense of hopelessness and subsequently increase the likelihood of completing education. This same reduced hopeless is then instrumentally linked to reduced onset of frailty. We encourage future researchers to consider these

pleitropic mechanisms but also the evocative rGE explanation in future work to better understand the cognitive, social, and psychological pathways through which genes associated with education may reduce the likelihood of frailty regardless of one's level of education.

Another key finding of our study was that the association between PGS_{educ} scores and frailty diminished with age. That is to say, genes related to educational attainment are more strongly predictive of frailty for participants in their 60's and 70's, and the effect was nearly absent beyond age 80. This is an important finding that is consistent with previous analyses of age trends in allostatic load (Crimmins et al., 2003), where age-related increases in allostatic load flattened at the oldest ages (Seeman et al. 2008). For education-related differences in physical performance tasks (e.g., grip strength, balance, walking speed, and chair stands), the effect also diminishes at advanced ages (80+ years). Given that the direct effect of education on health diminishes with age, we would expect that genes associated with education would also have less of an effect on health at advanced ages. Several explanations, ranging from sociological to biological, supporting this expectation have been put forth. First, differences in increasing risk of frailty with age have been documented across birth cohorts within the HRS (Yang and Lee, 2010). However, when birth cohorts were combined Yang and Lee (2010) found evidence that rates of frailty decrease with age. Secondly, phenotypic variation increases with age, thus any predictors of late-life/aging phenotypes weaken with progressing age. Rates of frailty were found to decrease with age, and it is well known that mortality rates slow at advanced ages (80+ years, Greenwood and Irwin 1939; Horiuchi and Wilmoth 1998; Thatcher 1999; Thatcher, Kannisto and Vaupel 1998; Gavrilova et al., 2017). Thirdly, this may reflect a survivor effect wherein those with worse physical function and lower education die at younger ages and are not included in the sample of aged participants (Welmer et al., 2013). Lastly, the relative importance of education on physical performance is less at older ages due to accumulation of deficits. Overall, the result that PGS_{educ} is less predictive of frailty beyond age 80

when birth cohorts are combined is supportive of the *age as leveler* hypothesis; although, attention should be paid to intracohort heterogeneity (Yang and Lee, 2010, Vaupel, Manton, Stallard, 1979).

There are several strengths of our study. While frailty is an easy concept to define, it is surprisingly difficult to measure and therefore, difficult to study. There is no consensus on the optimal way to measure frailty (Cigolle et al., 2009; Chao et al., 2018), however, there are two predominant clinical frailty metrics, the FI and the PLFI. The utility of these frailty metrics has been validated in different populations (Yang and Lee, 2010, Wu et al., 2018). While separate indices are not always convergent, they are often treated as complementary as they all are valid predictors of subsequent morbidity and mortality (Cesari et al., 2013, Theou et al., 2013b, Blodgett et al., 2015, Theou et al., 2015). A major strength of this study is that we use two frailty metrics and find converging evidence for the independent effect of the PGS_{educ}, above and beyond years of education, on frailty. Similarly, we find that both models of frailty support the *age as a leveler* hypothesis for the effects of genes associated with education across the life course. Finally, few studies have attempted to parse the effects of education from underlying genetic propensity for educational attainment. Unlike a majority of work, our study begins to disentangle this effect to illuminate possible underlying mechanisms.

Our study contributes to the larger body of work for studying the educational effects on aging, however, some limitations should be considered. We did not assess cohort differences in frailty dynamics. Others have shown that the genetic associations vary across birth cohort (Domingue et al. 2016) and historical periods (Boardman et al. 2010). Thus, the predictive power of a PGS in a replication sample may be attenuated with differences across studies in genotyping platforms, environmental contexts, or demographic characteristics (e.g., age, cohort, sex, or ethnicity, Wray et al., 2013, Ware et al., 2017, Tropf et al., 2017, Boardman et al., 2018). That is, the PGS_{educ} score may be most predictive in replication samples that closely match the discovery sample.

As the PGS was optimized for prediction in populations of European ancestry and may not replicated in other samples (Carlson et al., 2013, Martin et al., 2017), we too limited our sample. We encourage future work to evaluate comparable hypotheses with the full sample of respondents from the HRS.

Finally, we evaluated our hypotheses with men and women together. Others have shown gender differences in genetic associations with factors associated with frailty such as psychological resilience (Boardman et al. 2008). We simple controlled for gender in our models to but we did not specifically evaluate the possibility that these associations are systematically different as a function of gender identity. Compared to men, women tend to evidence higher levels of frailty, become frail earlier in the life course, but the effect of frailty on mortality is significantly less among women compared to men suggesting the composition of frail individuals may be very different for older men and women (Germain et al. 2016; Gordon et al. 2017) We encourage future work to consider the role of gender as a key mechanism linking education PGS, education, frailty, and survival.

References

Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., ... & Patsopoulos, N. A. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, *360*(6395), eaap8757.

Barth, D., Papageorge, N. W., & Thom, K. (2018). *Genetic Endowments and Wealth Inequality* (No. w24642). National Bureau of Economic Research.

Belsky, D. W., & Israel, S. (2014). Integrating genetics and social science: Genetic risk scores. *Biodemography and social biology*, *60*(2), 137-155.

Belsky, D. W., Moffitt, T. E., & Caspi, A. (2013). Genetics in population health science: strategies and opportunities. *American Journal of Public Health*, *103*(S1), S73-S83.

Belsky, D. W., Moffitt, T. E., Corcoran, D. L., Domingue, B., Harrington, H., Hogan, S., ... & Poulton, R. (2016). The genetics of success: How single-nucleotide polymorphisms associated with educational attainment relate to life-course development. *Psychological science*, *27*(7), 957-972.

Blodgett, J., Theou, O., Kirkland, S., Andreou, P., & Rockwood, K. (2015). Frailty in NHANES: comparing the frailty index and phenotype. *Archives of gerontology and geriatrics*, *60*(3), 464-470

Boardman, Jason D., Benjamin W. Domingue, and Jonathan Daw. 2015. What can genes tell us about the relationship between education and health? *Social Science & Medicine* 127:171-180.

Boardman, Jason D., Casey L. Blalock, and Tanya M.M. Button. 2008. Sex differences in the heritability of resilience. *Twin Research and Human Genetics* 11(1):12-27.

Branigan, A. R., McCallum, K. J., & Freese, J. (2013). Variation in the heritability of educational attainment: An international meta-analysis. *Social forces*, *92*(1), 109-140.

Brown DC, et al. (2012) The significance of education for mortality compression in the United States. Demography 49(3):819–840.

Bulik-Sullivan, B., Finucane, H. K., Anttila, V., Gusev, A., Day, F. R., Loh, P. R., ... & Daly, M. J. (2015). An atlas of genetic correlations across human diseases and traits. *Nature genetics*, *47*(11), 1236.

Carlson, Christopher S., Tara C. Matise, Kari E. North, Christopher A. Haiman, et al. 2013. "Generalization and Dilution of Association Results from European GWAS in Populations of NonEuropean Ancestry: The PAGE Study." PLoS Biology 11(9): e1001661

Cesari, M., Gambassi, G., Abellan van Kan, G., & Vellas, B. (2013). The frailty phenotype and the frailty index: different instruments for different purposes. *Age and ageing*, *43*(1), 10-12.

Chao, Y. S., Wu, H. C., Wu, C. J., & Chen, W. C. (2018). Index or illusion: The case of frailty indices in the Health and Retirement Study. *PloS one*, *13*(7), e0197859.

Christensen, Kaare, Gabriele Doblhammer, Roland Rau, and James W. Vaupel. "Ageing populations: the challenges ahead." *The Lancet* 374, no. 9696 (2009): 1196-1208.

Cigolle, C. T., Ofstedal, M. B., Tian, Z., & Blaum, C. S. (2009). Comparing models of frailty: the Health and Retirement Study. *Journal of the American Geriatrics Society*, *57*(5), 830-839.

Crimmins, E., Kim, J. K., & Vasunilashorn, S. (2010). Biodemography: New approaches to understanding trendsand differences in population health and mortality. *Demography*, *47*(1), S41-S64.

Dudbridge, F. (2013). Power and predictive accuracy of polygenic risk scores. PLoS Genetics, 9, 1003348.

Etman, A., Burdorf, A., Van der Cammen, T. J., Mackenbach, J. P., & Van Lenthe, F. J. (2012). Socio-demographic determinants of worsening in frailty among community-dwelling older people in 11 European countries. *J epidemiol community health*, *66*(12), 1116-1121.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., ... & McBurnie, M. A. (2001). Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(3), M146-M157.

Hagenaars, S. P., Harris, S. E., Davies, G., Hill, W. D., Liewald, D. C., Ritchie, S. J., ... & Worrall, B. B. (2016). Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N= 112 151) and 24 GWAS consortia. *Molecular psychiatry*, *21*(11), 1624.

Hamaker, ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systemic review. *Lance Oncol* (2012) 13:e347-e444

Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493737 UK Biobank participants *The Lancet* (2018) e323-32

Gandal, M. J., Haney, J. R., Parikshak, N. N., Leppa, V., Ramaswami, G., Hartl, C., ... & Liu, C. (2018). Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science*, *359*(6376), 693-697.

Germain, Cassandra M., Elizabeth Vasquez, John A. Batsis, and Douglas R. McQuoid. "Sex, race and age differences in muscle strength and limitations in community dwelling older adults: Data from the Health and Retirement Survey (HRS)." *Archives of gerontology and geriatrics* 65 (2016): 98-103.

Gordon, E. H., N. M. Peel, M. Samanta, O. Theou, S. E. Howlett, and R. E. Hubbard. "Sex differences in frailty: A systematic review and meta-analysis." *Experimental gerontology* 89 (2017): 30-40.

Gill, TM., Gahbauer, EA., Allore, HG., Han L. Transitions between frailty states among community-living older persons, *Arch. Intern. Med.* 2006 166:418:423

Goldman D, Culter D, Rowe JW, Michaud PC, Sullivan J, Peneva D, and Olshansky SJ. Substantial Health and Economic Returns from Delayed Aging May Warrant a New Focus for Medical Research (2013) Health Aff (Millwood) 32:1698-1705

Guo, Guang, and Hongxin Zhao. "Multilevel modeling for binary data." *Annual review of sociology* 26, no. 1 (2000): 441-462.

Jostins, L., & Barrett, J. C. (2011). Genetic risk prediction in complex disease. *Human molecular genetics*, *20*(R2), R182-R188.

Jung HW, Kim SW, Ahn S, Lim JY, Han JW, Kim TH, Kim KW, Kim KI, Kim CH.Prevalence and outcomes of frailty in Korean elderly population: comparisons of a multidimensional frailty index with two phenotype models PLoS One (2014) 9(2):e87958

Juster FT, Suzman R. An overview of the Health and Retirement Study. *Journal of Human Resources* 1995;30: S7-S56.

Lee, J. J., Wedow, R., Okbay, A., Kong, E., Maghzian, O., Zacher, M., ... & Fontana, M. A. (2018). Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nature genetics*, 1.

Martin, Alicia R., Christopher R. Gignoux, Raymond K. Walters, Genevieve L. Wojcik, Benjamin M. Neale, Simon Gravel, Mark J. Daly, Carlos D. Bustamante, and Eimear E. Kenny. 2017. "Human Demographic History Impacts Genetic Risk Prediction across Diverse Populations." American Journal of Human Genetics 100(4): 635–49

Marioni, R. E., Ritchie, S. J., Joshi, P. K., Hagenaars, S. P., Okbay, A., Fischer, K., ... & Amador, C. (2016). Genetic variants linked to education predict longevity. *Proceedings of the National Academy of Sciences*, *113*(47), 13366-13371.

Mitchell, U. A., Ailshire, J. A., Brown, L. L., Levine, M. E., & Crimmins, E. M. (2016). Education and psychosocial functioning among older adults: 4-year change in sense of control and hopelessness. *The Journals of Gerontology: Series B*, *73*(5), 849-859.

Mitnitksi A, Collerton J, Martin-Ruiz C, Jagger C, von Zglinicki T, Rockwood K, and Kirkwood T BL. Age-related frailty and its association with biological markers of aging *BMC Medicine* .

Mitnitski A, Mogliner AJ, and Rockwood K. Accumulation of Deficits as a Proxy Measure of Aging *The Scientific World* (2001) 1:323-336

Mitnitski, A., Song, X., & Rockwood, K. (2013). Assessing biological aging: the origin of deficit accumulation. *Biogerontology*, *14*(6), 709-717.

Mezuk, B., Lohman, M. C., Rock, A. K., & Payne, M. E. (2016). Trajectories of body mass indices and development of frailty: Evidence from the health and retirement study. *Obesity*, *24*(8), 1643-1647.

Okbay A, Beauchamp, JP, Fontana, MA, Lee, JJ, Pers, TH, Rietveld, CA, ... & Oskarsson, S (2016). Genome-wide association study identifies 74 loci associated with educational attainment, *Nature*, 533(7604), 539.

Patterson N, Price AL, Reich D. Population structure and eigenanalysis. *PLoS Genetics*. 2006;2: e190.

Paulson, D., & Lichtenberg, P. A. (2015). The Paulson–Lichtenberg Frailty Index: evidence for a self-report measure of frailty. *Aging & mental health*, *19*(10), 892-901.

Preston, S. H. (1984). Children and the elderly: Divergent paths for America's dependents. *Demography* 21(4): 435-457.

R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

RAND. 2014. "RAND HRS Data, Version N; RAND HRS Family Data Files, Version C. Produced by the RAND Center for the Study of Aging, with Funding from the National Institute on Aging and the Social Security Administration. Santa Monica, CA." Santa Monica, CA: RAND.

Rietveld, C. A., Conley, D., Eriksson, N., Esko, T., Medland, S. E., Vinkhuyzen, A. A., Esko, T., Medland, S. E., Vinkhuyzen, A. A. E., Yang, J., Boardman, J. D., Chabris, C. F., Daws, C. T., Domnigue, B. W., Hinds, D. A., Johannesson, M., Kiefer, A. K., Laibson, D., Magnusson, P. K. E., Mountain, J. L., Oskarsson, S., Rostapshova, O., Teumer, A., Tung, J. Y., Vissher, P. M., Benjamin, D. J., Cesarini, D., Koellinger, P. D., & the Social Science Genetics Association Consortium (2014). Replicability and robustness of genome-wide-association studies for behavioral traits. Psychological Science, 25, 1975-1986.

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal*, *173*(5), 489-495.

Rockwood K and Mitnitski A. Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty *Clin Geriatr Med* 27(2011) 17-26

Rodriguez-Manas L, Fried LP. Frailty in the clinical scenario *Lancet* (2014) 385:e7-e9.

Sanders, Jason L., Jatinder Singh, Ryan L. Minster, Jeremy D. Walston, Amy M. Matteini, Kaare Christensen, Richard Mayeux et al. "Association between mortality and heritability of the scale of aging vigor in epidemiology." *Journal of the American Geriatrics Society* 64, no. 8 (2016): 1679-1683.

Santos-Eggimann, Brigitte, Patrick Cuénoud, Jacques Spagnoli, and Julien Junod. "Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries." *The Journals of Gerontology: Series A* 64, no. 6 (2009): 675-681.

Seeman, T, Merkin SS, Crimmins E, Koretz B, Charette S, Karlamangla A. (2008) Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988-1994) *Social Science & Medicine*66:72-87

Sonnega A, Faul JD, Ofstedal MB, Langa KM. Phillips JW, Weir, DR. Cohort profile: the health and retirement study (HRS). *International Journal of Epidemiology*2014;43: 576-585.

StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.

Stretton, Caroline M., Nancy K. Latham, Kristie N. Carter, Arier C. Lee, and Craig S. Anderson. Determinants of physical health in frail older people: the importance of self-efficacy. *Clinical rehabilitation* 20, no. 4 (2006): 357-366.

Szanton, S. L., Seplaki, C. L., Thorpe, R. J., Allen, J. K., & Fried, L. P. (2010). Socioeconomic status is associated with frailty: the Women's Health and Aging Studies. *Journal of Epidemiology & Community Health*, 64, 63-67.

Theou, O., Brothers, T. D., Rockwood, M. R., Haardt, D., Mitnitski, A., & Rockwood, K. (2013). Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. *Age and ageing*, *42*(5), 614-619.

Theou, O., Brothers, T. D., Mitnitski, A., & Rockwood, K. (2013b). Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *Journal of the American Geriatrics Society*, *61*(9), 1537-1551.

Theou, O., Cann, L., Blodgett, J., Wallace, L. M., Brothers, T. D., & Rockwood, K. (2015). Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. *Ageing research reviews*, *21*, 78-94.

Tropf, F. C., Lee, S. H., Verweij, R. M., Stulp, G., van der Most, P. J., de Vlaming, R., ... & Iliadou, A. N. (2017). Hidden heritability due to heterogeneity across seven populations. *Nature human behaviour*, *1*(10), 757.

Vaupel, J. W., Manton, K. G., & Stallard, E. (1979). The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*, *16*(3), 439-454.

Visscher, P. M., Wray, N. R., Zhang, Q., Sklar, P., McCarthy, M. I., Brown, M. A., & Yang, J. (2017). 10 years of GWAS discovery: biology, function, and translation. *The American Journal of Human Genetics*, *101*(1), 5-22.

Wray, N. R., Yang, J., Hayes, B. J., Price, A. L., Goddard, M. E., & Visscher, P. M. (2013). Pitfalls of predicting complex traits from SNPs. *Nature Reviews Genetics*, *14*, 507- 515.

Ware, E. B., Schmitz, L. L., Faul, J. D., Gard, A., Mitchell, C., Smith, J. A., Zhao, W., Weir, D., & Kardia, S. L. (2017). Heterogeneity in polygenic scores for common human traits. *bioRxiv*, 106062.

Ware EB, Schmitz LL, Gard AM, Faul JD. HRS Polygenic Scores – Release 2. Ann Arbor, MI: Survey Research Center, Institute for Social Research, University of Michigan; 2018.

Welmer, Anna-Karin , Ingemar Kåreholt, Elisabeth Rydwik, Sara Angleman and Hui-Xin Wang. Education-related differences in physical performance after age 60: a cross-sectional study assessing variation by age, gender and occupation. *BMC Public Health* 2013 13:641

Wu, C., Geldhof, G. J., Xue, Q. L., Kim, D. H., Newman, A. B., & Odden, M. C. (2018). Development, Construct Validity, and Predictive Validity of a Continuous Frailty Scale: Results From 2 Large US Cohorts.

Yang Y and Lee LC (2010) Dynamics and Heterogeneity in the Process of Human Frailty and Aging: Evidence From the U.S. Older Adult Population *Journ of Geront: Social Sci* 65B:426-255

Young, Aideen CM, Karen Glaser, Timothy D. Spector, and Claire J. Steves. "The identification of hereditary and environmental determinants of frailty in a cohort of UK twins." *Twin Research and Human Genetics* 19, no. 6 (2016): 600-609.

Zajacova A, Hummer RA, Rogers RG (2012) Education and health among U.S. working- age adults: A detailed portrait across the full educational attainment spectrum. Biodemogr Soc Biol 58(1):40–61.

Zajacova, A., and J. K. Montez. 2017. Physical functioning trends among US women and men age 45–64 by education level. Biodemography and Social Biology 63 (1):21–30. doi:10.1080/19485565.2016.1263150.

Zajacova, Anna and Elizabeth M. Lawrence. 2018. The Relationship Between Education and Health: Reducing Disparities Through a Contextual Approach. *Annual Review of Public Health*, 39:273-28

Table 1. Descriptive statistics for all variables used in the analyses (n = 5,344)

	Mean/%	SD/N
Frailty Measures		
PL Score	1.23	1.18
PL Score > 3	0.15	828
Frailty Index	23.59	12.66
Frailty Index >=25	37.85	2023
Female	0.58	3106
Age (years)	74.66	6.86
Education (years)	13.04	2.55
Education PGS (z)	0.00	1.00
PC1 (z)	0.00	1.00
PC2 (z)	0.00	1.00
PC3 (z)	0.00	1.00
PC4 (z)	0.00	1.00
PC5 (z)	0.00	1.00

Note: Data come from the Health and Retirement Study (HRS).

Table 2. Bivariate associations between education PGS and frailty

	Quartile of Education PGS				
	Q1	Q2	Q3	Q4	pr. <
PL Score	1.29	1.25	1.19	1.18	0.001
PL Score > 3	17.08	15.39	14.77	14.68	0.025
Frailty Index	24.41	23.79	23.08	23.07	0.000
Frailty Index >=25	40.27	37.67	36.72	36.72	0.008

Note: Data come from the Health and Retirement Study (HRS).

Table 3. Education related genes and continuous indicators of frailty

	PL Frailty Index						Frailty 100 Index					
	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Female	0.34	(0.28, 0.39)	0.31	(0.26, 0.37)	0.32	(0.26, 0.37)	2.36	(1.75, 2.97)	2.10	(1.50, 2.71)	2.11	(1.51, 2.72)
Age	0.29	(0.26, 0.31)	0.28	(0.26, 0.30)	0.28	(0.25, 0.30)	3.49	(3.27, 3.70)	3.40	(3.18, 3.61)	3.39	(3.18, 3.60)
PC1	-0.01	(-0.04, 0.01)	-0.01	(-0.04, 0.01)	-0.01	(-0.04, 0.01)	-0.04	(-0.35, 0.26)	-0.02	(-0.32, 0.28)	-0.02	(-0.32, 0.28)
PC2	0.01	(-0.02, 0.03)	0.01	(-0.01, 0.04)	0.01	(-0.01, 0.04)	0.22	(-0.08, 0.52)	0.26	(-0.04, 0.56)	0.26	(-0.04, 0.56)
PC3	0.00	(-0.03, 0.02)	-0.01	(-0.03, 0.02)	-0.01	(-0.03, 0.02)	-0.18	(-0.49, 0.12)	-0.26	(-0.56, 0.04)	-0.26	(-0.56, 0.04)
PC4	-0.01	(-0.04, 0.02)	-0.01	(-0.04, 0.02)	-0.01	(-0.04, 0.02)	-0.13	(-0.43, 0.18)	-0.15	(-0.44, 0.15)	-0.14	(-0.44, 0.15)
PC5	0.04	(0.01, 0.06)	0.04	(0.01, 0.06)	0.04	(0.01, 0.06)	0.57	(0.27, 0.87)	0.56	(0.26, 0.86)	0.56	(0.26, 0.86)
Education PGS	-0.06	(-0.09, -0.04)	-0.03	(-0.06, -0.01)	-0.03	(-0.06, 0.00)	-0.84	(-1.14, -0.54)	-0.44	(-0.75, -0.13)	-0.41	(-0.72, -0.10)
Education			-0.13	(-0.16, -0.10)	-0.13	(-0.16, -0.1)			-1.67	(-1.98, -1.36)	-1.67	(-1.98, -1.36)
PGS*Age					0.03	(0.00, 0.05)					0.24	(0.02, 0.45)
Intercept	1.05	(1.01, 1.09)	1.06	(1.02, 1.10)	1.06	(1.02, 1.10)	22.46	(21.99, 22.93)	22.63	(22.17, 23.09)	22.61	(22.15, 23.08)
level 1	0.83	(0.82, 0.84)	0.83	(0.76, 0.81)	0.83	(0.82, 0.85)	7.22	(7.11, 7.34)	7.23	(7.12, 7.34)	7.23	(7.12, 7.34)
level 2	0.79	(0.77, 0.82)	0.78	(0.76, 0.81)	0.78	(0.76, 0.81)	10.07	(9.83, 10.31)	9.93	(9.69, 10.17)	9.92	(9.69, 10.16)
Error Variance												
Level 1	0.69	(0.67, 0.71)	0.69	(0.58, 0.65)	0.69	(0.67, 0.71)	52.20	(50.58, 53.86)	52.26	(50.64, 53.92)	52.26	(50.65, 53.93)
Level 2	0.63	(0.59, 0.67)	0.61	(0.58, 0.65)	0.61	(0.58, 0.65)	101.41	(96.69, 106.37)	98.59	(93.97, 103.45)	98.45	(93.83, 103.30)
Rho	0.48		0.47		0.47		0.66		0.65		0.65	

Note: Data come from the Health and Retirement Study. Cell entries represent parameter estimates from a multilevel model in which observations are nested within individuals. Values in parentheses represent 95% confidence intervals.

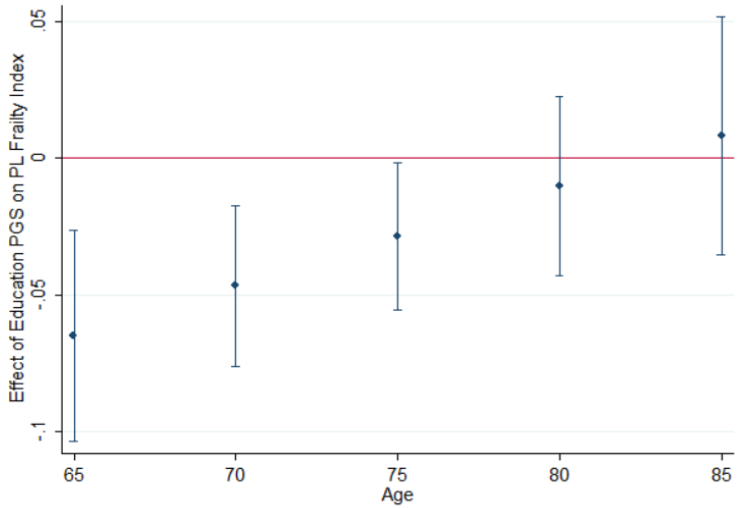
Table 4. Education related genes and binary indicators of frailty

	PL Frail						Frail 100 Index					
	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Female	0.99	(0.79, 1.19)	0.94	(0.74, 1.14)	0.94	(0.74, 1.14)	0.70	(0.50, 0.90)	0.63	(0.43, 0.82)	0.63	(0.44, 0.83)
Age	0.79	(0.69, 0.88)	0.76	(0.67, 0.85)	0.76	(0.67, 0.85)	0.86	(0.77, 0.94)	0.82	(0.73, 0.91)	0.82	(0.73, 0.91)
PC1	-0.02	(-0.11, 0.07)	-0.01	(-0.11, 0.08)	-0.01	(-0.11, 0.08)	0.01	(-0.09, 0.10)	0.01	(-0.08, 0.11)	0.01	(-0.09, 0.11)
PC2	0.01	(-0.08, 0.11)	0.02	(-0.07, 0.12)	0.02	(-0.07, 0.12)	0.04	(-0.06, 0.13)	0.05	(-0.05, 0.15)	0.05	(-0.05, 0.15)
PC3	-0.02	(-0.12, 0.07)	-0.04	(-0.13, 0.05)	-0.04	(-0.13, 0.05)	0.02	(-0.08, 0.12)	0.00	(-0.10, 0.10)	0.00	(-0.10, 0.10)
PC4	-0.02	(-0.12, 0.07)	-0.03	(-0.12, 0.07)	-0.03	(-0.12, 0.07)	-0.02	(-0.12, 0.07)	-0.03	(-0.12, 0.07)	-0.03	(-0.12, 0.07)
PC5	0.17	(0.08, 0.27)	0.17	(0.07, 0.27)	0.17	(0.07, 0.27)	0.19	(0.09, 0.29)	0.19	(0.09, 0.29)	0.19	(0.09, 0.29)
Education PGS	-0.16	(-0.26, -0.07)	-0.07	(-0.16, 0.03)	-0.08	(-0.18, 0.00)	-0.21	(-0.31, -0.11)	-0.09	(-0.19, 0)	-0.08	(-0.18, 0.00)
Education			-0.40	(-0.50, -0.30)	-0.40	(-0.50, -0.30)			-0.49	(-0.59, -0.39)	-0.49	(-0.59, -0.39)
PGS*Age					0.11	(0.03, 0.19)					0.14	(0.07, 0.22)
Intercept	-3.51	(-3.74, -3.29)	-3.49	(-3.71, -3.27)	-3.50	(-3.72, -3.28)	-1.40	(-1.56, -1.24)	-1.36	(-1.51, -1.2)	-1.37	(-1.53, -1.21)
Error Variance												
Level 2	4.77	(4.08, 5.58)	4.64	(3.97, 5.44)	4.61	(3.94, 5.4)	7.71	(6.89, 8.64)	7.47	(6.66, 8.38)	7.46	(6.65, 8.36)
Rho	0.59		0.59		0.58		0.70		0.69		0.69	

Note: Data come from the Health and Retirement Study. Cell entries represent parameter estimates from a multilevel model in which observations are nested within individuals. Values in parentheses represent 95% confidence intervals.

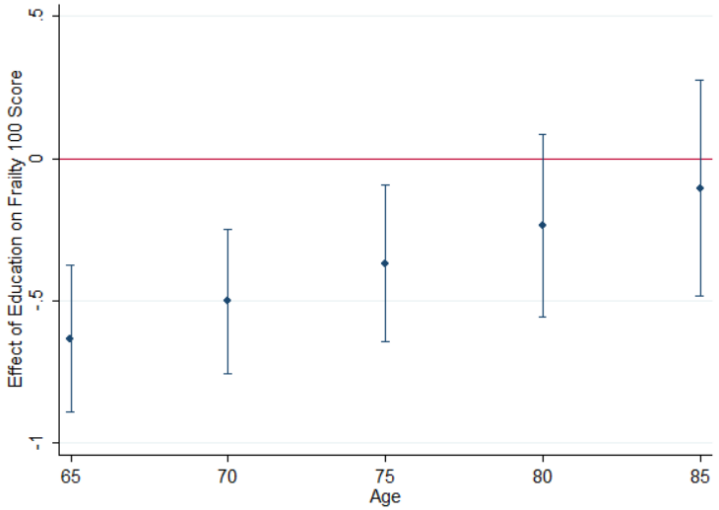
PGS_{educ}, Education, & Frailty

Figure 1a. PGS*Age interaction PL Frailty



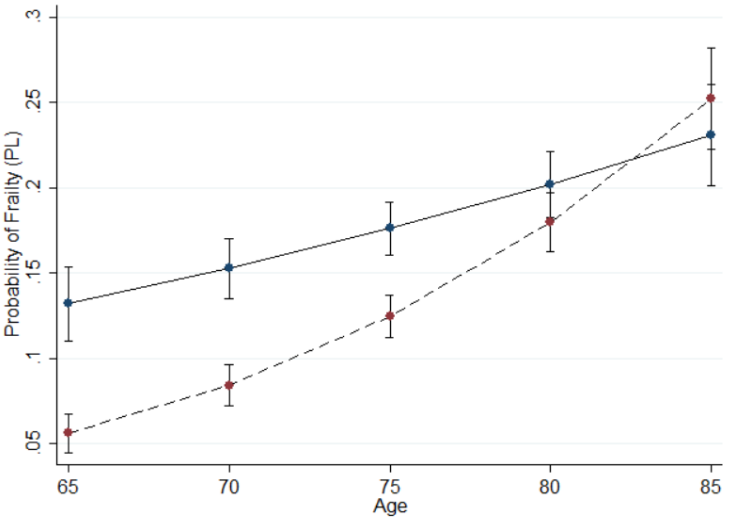
Note: Estimates derived from Table 3 Model 3.

Figure 1b. PGS*Age interaction Frail 100 Index



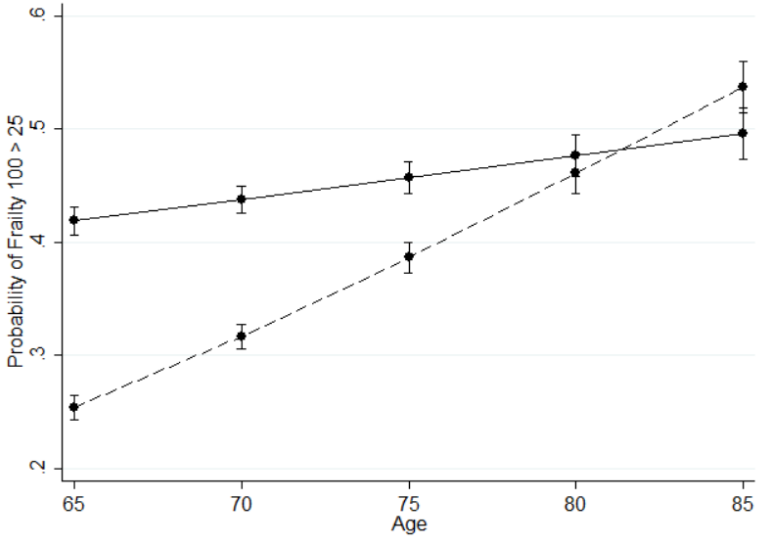
Note: Estimates derived from Table 3 Model 6.

Figure 1c. PGS*Age interaction on risk of frail status (PL)



Note: Estimates derived from Table 4 Model 3.

Figure 1d. PGS*Age interaction on risk of frail status (F100)



Note: Estimates derived from Table 4 Model 6.