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Keywords: Education, Mortality, Disparities, Twins

Education is known to have a graded relationship with morbidity and mortality globally. The education/mortality gradient has been growing steeper as income inequality and educational disparities have been growing in the United States. However, much less is known about temporal trends in this relationship in more equitable countries with larger safety nets and lower levels of income inequality. Further, prior estimates of the educational gradient may be biased by family background and genetic effects that have been ignored in most population-based analyses. Our analysis seeks to explore temporal changes in the education/mortality gradient in countries other than the United States (Sweden, Australia, and Finland) using several harmonized cohorts of twins in the Consortium on Interplay of Genes and Environment across Multiple Studies (IGEMS). Findings show that while education/mortality gradients are largely robust to inclusion of controls for both family background and genetics, there is no evidence that these gradients are growing steeper in Sweden, Australia, and Finland, but rather, remain consistent across a wide range of historical birth cohorts.

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Genetic Architecture of Self-rated Health: Relationship with Physical Health, Cognition Function, and Depression

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Keywords: Self-rated health, Depression, Cognition, Physical health, Age differences

The fact that self-rated health (SRH) predicts mortality and a variety of other health outcomes independent of objective health measures generates questions about mechanisms and etiologies. SRH can be considered an indicator of physical health, per se, resulting from active cognitive processing of explicit information about one's own health and intuitive knowledge of symptoms and physical sensations. The extent to which SRH taps shared cultural ideas about health should be reflected in estimates of the shared environmental component of variance (C). SRH has also been associated with emotional health measures, such as neuroticism and depression. Previous analyses have been limited by sex (only women), sample size, age (range = 63–76), and failure to include cognitive function (Leinonen et al., 2005). The current analysis used data from 10,682 adults ranging in age from 22 to 102 from the international Interplay of Genes and Environment Across Multiple Studies (IGEMS) consortium to investigate the genetic architecture of SRH. Independent pathways model of SRH included CIRS (Cumulative Illness Rating Scale), MMSE (Mini-Mental Status Exam), and depression (CES-D or CAMDEX), with age, sex, and country included as covariates. All genetic variance for SRH was shared with CIRS, MMSE, and depression. Comparison of groups older and younger than 74 indicated age differences in genetic architecture of SRH. Evidence suggests that the discordance between objective and subjective health increases in late adulthood, possibly as a result of greater emphasis on psychological rather than physical components of subjective health assessments by older adults.

References: Leinonen R Kaprio J Jylhä M Tolvanen A Koskenvuo M Heikkinen E Rantanen T (2005) Genetic influences underlying self-rated health in older women. JAGS 53:1002–7.

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Adjusting for Genetic Confounding Using Polygenic Scores Within Structural Equation Models

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Keywords: Genetic confounding, Polygenic scores, Structural equation models

Associations between exposures and outcomes in observational research are prone to unobserved confounding, including arising from genetic effects on exposures and outcomes. Researchers have started adjusting for genetic confounding using polygenic scores. However, adjustment using polygenic scores can be insufficient due to measurement error. Here we build on previous work (Pingault et al., 2021) combining measured genetic variants and heritability estimates from twin- and genome-wide association studies using structural equation modelling (SEM). We developed a method that enables adjustment for genetic confounding in the association between multiple continuous exposures and an outcome of interest. Our method is implemented in R software, allowing raw data and covariance matrices as input and a range of estimators including bootstrapping for indirect effects. We provide estimates for genetic confounding, genetic overlap, and environmentally mediated genetic effects. Simulations using both simulated polygenic scores and SNP data show that our method accurately captures genetic confounding in the exposure-outcome associations. We show that estimated quantities are largely unbiased even under model misspecification, e.g. residual correlation between exposures. Under misspecifications however, environmentally mediated genetic effects should be interpreted carefully. The nature of SEM will enable further extensions to non-continuous data and other models.

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GENETIC ARCHITECTURE OF SUBJECTIVE HEALTH: RELATIONSHIP WITH PHYSICAL HEALTH, COGNITION, AND DEPRESSION

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CONCLUSIONS

- Age 50-74: all variance in SRH shared with physical, cognitive, and emotional health
- Age 75-100: some genetic variance unique to SRH
- Age differences in correlations and genetic contributions to correlations between SRH and physical, cognitive, and emotional health

Discordance between objective and subjective health increases in late adulthood,[1] possibly as a result of greater emphasis on psychological rather than physical components of SRH in older adults.[2]

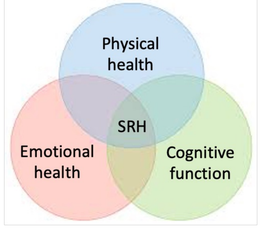
INTRODUCTION

Subjective health is an indicator of **physical health** and

- Active **cognitive** processing of info about one's health[3]
- Intuitive knowledge about symptoms & physical sensations[4]
- Culturally-influenced concepts of "health"[5]
- **Emotional** measures including neuroticism and depression[6]

Research Questions:

- To what extent are genetic and environmental influences on SRH shared with physical, emotional, and cognitive health?
- Do these relationships vary with age?



METHODS

Interplay of Genes and Environment across Multiple Studies (IGEMS) Consortium[7]

- 8 twin studies across 4 countries: Australia, Sweden, Denmark, United States (N = 8291)
- Age range = 22-102 (35% female)

Measures

- Self-Rated Health (**SRH**): standardized within study
- Physical Health: Cumulative Illness Rating Scale (**CIRS**) harmonized across studies
- Cognitive Health: Mini-Mental Status Exam (**MMSE**) or Telephone Interview for Cognitive Status, standardized within study at cut-off for cognitive impairment
- Depressive Symptoms (**DEPR**): CES-D or CAMDEX harmonized across studies

RESULTS

Heritability of SRH = 32%

Figure 1: Genetic variance specific to SRH only in older

Figure 2: Correlations with SRH

- Correlation with physical health did not differ across age group
- Correlations with Depression and MMSE higher in older group
- Variable and age group differences in extent to which correlations arose from common genetic sources.

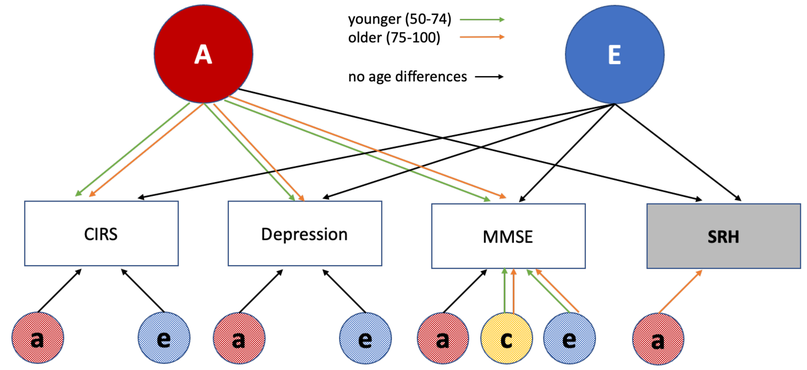


Figure 1. Independent pathways model decomposing variance into shared genetic (A) and environmental (E) variance and independent genetic (a), common env. (e) and unique env. (e) variance – for younger (50-74) and older (75-100) adults. Corrected for sex , country & age.

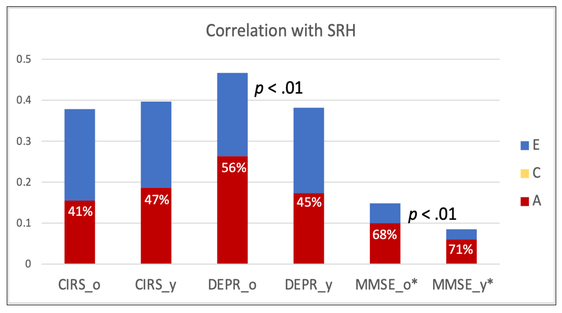


Figure 2. Higher scores on SRH indicate worse health. Percentages indicate % of correlation arising from common genetic variance. Corrected for sex & country & age (within group).
_o indicates older (75-100)
_y indicates younger (50-74)
*MMSE is reverse scored

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LINK TO POSTER

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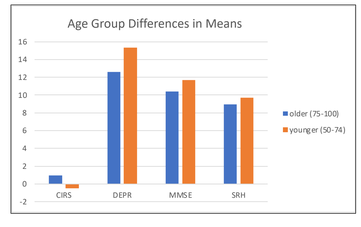

Higher scores =
CIRS: more health issues
DEPR: more symptoms
MMSE: better cognition
SRH: worse health
All means significantly different across age groups at $p<.01$. Corrected for sex, country, and age (within group)