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Genomic Psychiatry

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Shared genetic etiology between childhood cognitive function and longevity

Genomic Psychiatry; https://doi.org/10.61373/gp025l.0098

Cognitive function and longevity are phenotypically and genetically correlated. Whereas molecular genetic data have been used to show that adult cognitive function is genetically correlated with longevity, no such analysis has examined the association between childhood cognitive function and longevity. Using genome-wide association study data on childhood cognitive function (n = 12,441) and on parental longevity (n = 389,166) we found a positive genetic correlation of $r_g = 0.35$ (SE = 0.14, $P = 0.01$) between childhood cognitive function and parental longevity. These results add to the weight of evidence that the phenotypic link between childhood cognitive function and longevity is partly accounted for by shared genetic etiology.

The goal of the research field of cognitive epidemiology (1, 2) is to describe and explain phenotypic associations between cognitive function tested in youth (which largely avoids reverse causation) and later-life health and death. Analyses of long-term follow-up data from large cohorts sourced from the UK, Denmark, Israel, and Sweden show that higher scores on cognitive function tests in youth (childhood, adolescence, or young adulthood) are associated with lower risk of mortality from all causes by mid to late adulthood (2). A systematic review of 16 separate studies, drawing data from over 1 million participants (22,453 deaths) found that, on average, for a 1 standard deviation higher cognitive function test score in youth, there was a 24% (95% CI = 23–25) lower risk of death during a follow-up period of between 17 and 69 years (3).

What causes this association? The cognition-longevity relationship was not confounded by childhood socioeconomic position, was present across a range of cognitive ability, and was present in both men and women (3). There was some attenuation by education and the person's own adult occupational social class.

Might part of the cognition-longevity association be caused by genetic differences? Large genome-wide association studies (GWASs) have been conducted to examine the molecular genetic etiology of people's differences in cognitive function test scores (4, 5). There are also GWASs on longevity (6). These GWAS data enable a comparison between traits; that is, one may compare the loci that attain genome-wide statistical significance in cognition with those that are genome-wide significant in longevity. Furthermore, a genetic correlation between these two traits' GWASs can be derived to describe their average shared genetic effect. One estimate of the genetic link between cognitive function and longevity (obtained by reversing all-cause mortality) is $r_g = 0.37$, SE = 0.06, $P = 0.009$ (4).

However, unlike phenotypic analyses, in which childhood cognitive function is used as a predictor of longevity up to old age, genetic correlations between these variables have been derived using cognitive function assessed in adulthood and older age. This leaves unanswered the question of whether reverse causation/confounding (i.e., that poor health in adulthood and later life influences both cognitive function and longevity) drives some of the genetic association between cognitive function and longevity. The genetic correlation between cognitive function in childhood and cognitive function in adulthood/older age is high but imperfect ($r_g = 0.71$, SE = 0.10) (7). Moreover, the genetic relationship between cognitive function and some health outcomes is dependent on the age at which cognitive function was measured (7).

To date, we are not aware of any genetic correlation having been reported between cognitive function tested in childhood and longevity. In order to address this lacuna in cognitive epidemiology, we use data from two GWASs to estimate the genetic correlation between cognitive function assessed in childhood (8) and longevity (combined mothers' and fathers' attained age) (6).

Applying linkage disequilibrium score regression (for further details see supporting online material) to these GWASs' data, we find that the single nucleotide polymorphism (SNP)-based heritability of childhood cognitive function was 27.3% (SE = 4.7) and the heritability of parental longevity was 28.9% (SE = 0.7). The linkage disequilibrium score regression (LDSC) intercepts for both childhood cognitive function and longevity were close to 1 indicating little inflation due to population stratification.

The principal result from the present analysis is that the genetic correlation between childhood cognitive function and combined-parental attained years was $r_g = 0.35$ (SE = 0.14, $P = 0.01$). This indicates that some of the genetic variants associated with higher childhood cognitive function are also associated with one's parents' living longer.

The current results contribute toward filling a gap in our understanding of cognitive epidemiology and show that, in the absence of reverse causality/confounding, pleiotropy might provide a partial explanation for the phenotypic link between cognitive function and longevity (2).

A limitation of this work is that the presence of a genetic correlation between childhood cognitive function and longevity is consistent with a number of models of pleiotropy, each describe a different genetic relationship between traits that cannot be distinguished from each other with the methods used here. We discuss two forms of pleiotropy below and outline what this would mean for the relationship between cognitive function and longevity.

First, genetic correlations can arise due to horizontal pleiotropy. Horizontal pleiotropy describes instances in which a genetic variant (or group of variants) has two independent effects on the two phenotypes that are genetically correlated. Should horizontal pleiotropy be one of the drivers of this genetic link between cognitive function and longevity, then it would be evidence for the "system integrity" hypothesis, i.e., that more intelligent people tend to live longer and in better health due, in part, to genetic effects producing a body and brain more capable of withstanding environmental insults (9).

Second, the presence of a genetic correlation can sometimes be explained by vertical pleiotropy. Vertical pleiotropy describes instances where two phenotypes are genetically correlated as a consequence of one phenotype's being causally related to the second. In this type of pleiotropy, the genetic correlation between childhood cognitive function and longevity may have arisen, in part, due to childhood cognitive function's providing entry into environments more likely to be conducive to good health. For example, cognitive function has been found to be causally related to education (10) and

Received: 18 July 2025. Revised: 30 September 2025. Accepted: 1 October 2025.

a higher level of education is associated with a higher level of socioeconomic position and less material privation and a greater tendency toward healthier behaviors and higher health literacy.

Furthermore, the genetic correlation derived herein describes the average shared genetic effect across the autosomes. It does not provide information pertaining to which regions of the genome (beyond the autosomal contributions) contribute to this effect. As such, it is of limited utility in understanding the shared biological systems (if any) that are linked to the observed genetic correlation. Additional work is required to identify regions of the genome that drive this genetic correlation.

Funding sources

WDH is supported by a Career Development Award from the Medical Research Council (MRC) [MR/T030852/1] for the project titled "From genetic sequence to phenotypic consequence: genetic and environmental links between cognitive ability, socioeconomic position, and health". IJD is supported by grants from the National Institutes of Health (NIH) (R01AG054628 and U01AG083829) and by BBSRC and ESRC (BB/W008793/1).

Author disclosures

The authors have no conflicts of interest to disclose.

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