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Estimating the parental age effect on intelligence with controlling for confounding effects from genotypic differences

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ABSTRACT

The association between parental age at conception and children's traits has often been studied as it may reflect germline *de novo* mutation accumulation and is expected to be monotonic negative. However, for IQ, the relationship has often been found to be inverted U-shaped, possibly because of confounding by parental characteristics that correlate with child-bearing age. Here, I leverage polygenic scores (PGS) as an indirect measure of parental intelligence and examine how the effect changes as the explanatory power increase to heritability. Heritability can be estimated by calculating the phenotype variance explained by the genetic effect when the paternal-maternal ratio of the projected age effects after controlling the genetic effect matches the male-female ratio of mutation rate. After controlling for PGS and demographic factors, I estimate a −2.0 (95 % CI, −0.3 to −3.7) IQ points change in intelligence per decade rise in paternal age. After further adjustment for birth order, it declined to −0.6 (−2.6 to 1.6). Even if only the latter estimate is attributable to mutation accumulation, the result would imply a substantial contribution of *de novo* mutations in the variance of intelligence. However, the association might not equal the effect of *de novo* mutations and further studies are needed.

1. Introduction

The association between parental age, especially paternal age, at conception and children's traits has drawn considerable academic interest because it may provide valuable insights into the effect of *de novo* mutations. For males, about two germline single-nucleotide mutations are introduced every year (Kong et al., 2012). For females, the number of *de novo* germline mutations is smaller than for males but also increases with age. The ratio of male to female germline single-nucleotide and indel mutations (denoted as α) is constant at about 3–4:1 (Gao et al., 2019).

Studies have examined the impact of parental age on monogenic diseases and neurodevelopmental disorders, with many finding a negative impact of parents' age on children's health (Bergh et al., 2019; Nybo Andersen & Urhoj, 2017). Huguet et al. (2021) estimate that around half of all genes negatively affect intelligence when deleted. If this is so, it is reasonable to expect *de novo* mutations that damage the function of genes would have a negative effect on intelligence, which is historically subjected to purifying selection (Woodley of Menie, 2015). However, the effect of parental age on children's cognitive ability has been less clear despite a substantial amount of research. The accumulation of *de novo* mutations is monotonic and close to linear (Kong et al., 2012) but the observed parental age effect is nonlinear in some analyses, with individuals given birth to by parents around their thirties having higher intelligence than those by teenage and old parents. In addition to such inverted U-shaped relationship, studies using different sample and analysis designs give monotonically positive or negative associations (Carslake et al., 2017; Gajos & Beaver, 2017; Malaspina et al., 2005; McGrath et al., 2013; Myrskylä et al., 2013; Saha et al., 2009; Whitley et al., 2012).

The parental age effect on intelligence could be associated with many factors: (1) Biological factors: increased parental age is associated with an increased mutation load, epigenomic alternations and an adverse *in-utero* environment. (2) Psychosocial factors: older parents are more experienced and mature and they offer more resources to children. (3) Selection effect: more able parents tend to give birth to children at an older age. The nonlinear inverted U-shaped relationship observation might be the result of the combination of the generally negative effect from biological factors and the generally positive effect from the psychosocial factors and the selection effect associated with an older parental age. To control for the selection effect, a direct way is to control for the parental phenotype. For example, Arslan et al. (2014) tested the paternal age effect on intelligence after controlling for parents' trait levels and found an initially positive association turned non-

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significantly negative. However, parental traits related to cognitive ability are often not collected in longitudinal studies. Even when they are recorded, data collection could be subject to selection bias (Arden et al., 2016) if cognitive tests were administered, and might be less accurate if a proxy phenotype were used. Educational attainment has been widely used as a proxy phenotype for the trait (Hill et al., 2019) because of its high genetic correlation with cognitive ability and is widely collected; but education could reflect traits other than intelligence, such as diligence.

It is useful to distinguish between two kinds of mutations: old mutations (polymorphisms) that have become common in the population, and recent mutations that arose recently in the population as germline *de novo* mutations. Genome-wide association studies (GWAS) identify the former kind and many were performed for educational attainment or cognitive ability recently. Despite the use of data from 1.1 million individuals in the largest GWAS of educational attainment, the resulting polygenic score (PGS) can explain only a small proportion of the variance in educational attainment (11–13 %) and IQ (7–10 %) (Lee et al., 2018). It is possible that recent mutations are responsible for much of the "missing heritability", but we still don't know how much. *de novo* mutations are random, and the chance of affecting a tag variant is very small. This indicates that because children's PGS is calculated with common polymorphisms (unaffected by *de novo* mutations), the PGS can be used as a control for the confounding effects of parents' intelligence influence on children. By doing so, the effect of rising parental age itself could be isolated from the effect of parental intelligence. However, because of missing heritability, the effect could only be partially controlled. Adjustment is required for full control of the parental effect.

To estimate the effect of parents' age on children's cognitive ability after controlling for the effect of the child's PGS and thereby indirectly also for parental characteristics, the present study use data from the Wisconsin Longitudinal Study (Hauser et al., n.d., N = 4692), with data from the Health and Retirement Study (Health and Retirement Study, 2022, N = 9369) as replication with the trait educational attainment.

2. Materials and methods

2.1. Statistical analysis

In the analysis, I first estimated the parental age effects on intelligence after controlling for each of the available PGS to remove confounding effects from genotype. However, even the most powerful PGS only explains a portion of the heritability of intelligence, so this removal is incomplete. Fig. 1 shows a plot of parental age effects (y-axis) against the explanatory power of the PGS (x-axis). To fully remove the confounding effect, it is necessary to control for the full heritability of intelligence. To make this estimate, I assumed that the relationship between the estimated parental effects and the variance of intelligence explained by the PGS would still hold even after using the most powerful PGS. I then fitted a line through the available data points. At the point where the variance of intelligence explained (x-axis) equals the heritability of intelligence, the confounding effect on parental age effects should be fully removed (y-axis). To estimate how much variance explained (heritability) of intelligence should be used in the estimation, I assumed the ratio of paternal and maternal effects should match the ratio of male and female *de novo* mutation rates. When this condition was met, the variance of intelligence explained was taken as a new estimate of heritability, and the age effects were taken as the effects with genotype confounding removed. This analysis was repeated for the trait of years of education.

2.2. α estimate

Gao et al.'s (2019) binomial logistic regression estimation of α (averaged over parental age) of 719 Icelandic trios was 3.50 and 3.62 for ages 20 and 40, respectively (Gao et al., 2019). The average value of 3.56 was used in the present study.

3. Results

R^2 and incremental R^2 of each PGS in regressions predicting intelligence and the years of education are shown in Table 1. The table shows

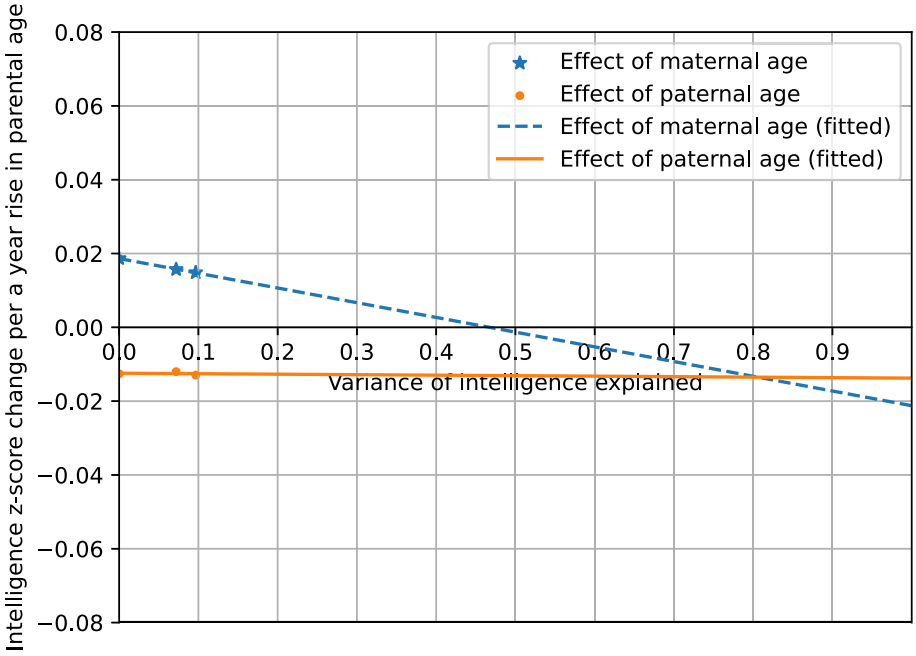

Fig. 1. The explanatory powers of the PGS on intelligence (heritability) and the effects of parental age on intelligence.
Note: Z-scores of the years of education standardised by age and gender was used as the target variable in the regression. Gender, birth year, their interaction term, age of both parents and genetic principal components were adjusted in all models.

Table 1
Model R^2 and incremental R^2 in regressions of each PGS on YOE.

PGS	Model R^2	Incremental R^2 relative to base
Dataset: Wisconsin Longitudinal Study, phenotype: intelligence, unadjusted for birth order		
PGS_base	0.013	0.000
pgs_cp_gwas	0.084	0.072
pgs_cp_mtag	0.109	0.097
Dataset: Wisconsin Longitudinal Study, phenotype: intelligence, adjusted for birth order		
PGS_base	0.012	0.000
pgs_cp_gwas	0.084	0.073
pgs_cp_mtag	0.110	0.098
Dataset: Wisconsin Longitudinal Study, phenotype: years of education, unadjusted for birth order		
PGS_base	0.029	0.000
pgs_ea3_mtag	0.098	0.069
pgs_ea3_gwas	0.098	0.069
Dataset: Wisconsin Longitudinal Study, phenotype: years of education, adjusted for birth order		
PGS_base	0.030	0.000
pgs_ea3_gwas	0.097	0.068
pgs_ea3_mtag	0.098	0.068
Dataset: Health and Retirement Study, phenotype: years of education, unadjusted for birth order		
PGS set 1 base	0.006	0.000
E4_EDU2_SSGAC16	0.067	0.061
E4_EDU3_SSGAC18	0.087	0.082
E4_EA3_W23_SSGAC18	0.093	0.087
PGS set 2 base	0.005	0.000
PGS_EA3_GWAS	0.124	0.120
PGS_EA3_MTAG	0.131	0.126

Note: Z-scores of intelligence and YOE standardised by age and gender was used as the target variable in the regression. Gender, birth year, their interaction term and PCs were adjusted in all models. To control for birth order in some analysis, birth order was also involved in the standardisation and regression model.

that the best-performing PGS can explain a tenth of the trait in the present sample.

To see if PGS of cognition confounds the effect of parental age on intelligence, I've constructed models predicting intelligence with parental ages and each of the PGS and the one without PGS. The explanatory powers of the PGS on intelligence and the effects (beta) of parental age on intelligence were plotted in Fig. 1. The figure shows how parental age effects would change as the variance of intelligence explained by PGS changes. As we can see, although when the variance explained is 0 (not controlling for parental PGS) the effect was in the opposite direction, the fitted line gradually come close and finally crossed each other. The plot was replicated using the variable years of education from the same dataset and the Health and Retirement Study. For the Wisconsin Longitudinal Study, results from regression involving birth order as a term were also plotted. The plots were shown in Figs. S1–S4. They all show a similar pattern.

There is a gap between the largest variance explained by PGS (9.7 %) and the family-based heritability (at least 50 %), which means controlling for any of the available PGS is not enough to take account of parental confounding. Because it is the phenotype that directly influences the age at reproduction, the underlying genotype, no matter whether captured by PGS or not, should influence the age at reproduction in the same way. Therefore, when the variance explained matches the full heritability, we can take the projected value of the effect as the true effect of increasing parental age. Similar approaches were employed in earlier studies (Beauchamp, 2016; Pingault et al., 2021). However, how much exactly should the heritability be taken? We can take advantage of the fact that the ratio of *de novo* mutation rate between males and females is known and the relative strengths of paternal age and maternal age effects should match the ratio. When they match, the proportion of variance explained is a new estimate of heritability. When estimating the effects, heritability estimated in this way was used.

Heritability and parental age effect estimates are shown in Table 2.

To see if the confounding was removed by controlling for PGS, average differences in intelligence for each parental age from the all-age average were calculated and shown in Fig. 2. In the unadjusted subplots, raw differences in intelligence were shown. In the subplots adjusted for PGS, average PGS differences (z-score) for each parental age from the all-age average adjusted by heritability (h^2) were subtracted from the raw intelligence differences (IQ, z-score).

$$IQ_{diff\ ,adjusted} = IQ_{diff} - \frac{PGS_{diff}}{R^2_{incremental}/h^2}$$

PGS showing the largest incremental R^2 was used. The relationship was shown in Fig. 2. Replications using the years of education are shown in Figs. S5 and S6. As we can see, the unadjusted relationships are inverted U-shaped or monotonic positive, which replicates the results of other analyses that did not control for parental characteristics (Carslake et al., 2017; Gajos & Beaver, 2017; Malaspina et al., 2005; McGrath et al., 2013; Myrskylä et al., 2013; Whitley et al., 2012). After the adjustment for PGS, relationships turned monotonically negative for both mother and father.

4. Discussion

In the present study, I have examined the impact of parental age on intelligence. The analysis addressed the issue of the confounding effects of parental genotype by controlling for PGS innovatively. The method was robust as shown by examining two independent datasets. I have proposed a new way of estimating heritability by calculating the phenotype variance explained by the genetic effect when the paternal-

Table 2
Sample size, parental age effects after controlling for PGS and heritability estimates.

Phenotype	PGS set	Sample size	Paternal effect[a] (95 % CI)	Maternal effect[a] (95 % CI)	Heritability[b] (95 % CI)
Dataset: Wisconsin Longitudinal Study, unadjusted for birth order					
Intelligence	–	4692	−0.013 (−0.025 to −0.002)	−0.004 (−0.017 to 0.009)	0.560 (0.297 to 1.473)
Years of edu	–	7248	−0.015 (−0.025 to −0.006)	−0.004 (−0.015 to 0.006)	0.494 (0.324 to 0.905)
Dataset: Wisconsin Longitudinal Study, adjusted for birth order					
Intelligence	–	4673	−0.004 (−0.018 to 0.011)	−0.001 (−0.018 to 0.014)	0.726 (0.421 to 2.076)
Years of edu	–	4602	−0.010 (−0.022 to 0.005)	−0.003 (−0.018 to 0.011)	0.586 (0.332 to 1.426)
Dataset: Health and Retirement Study, unadjusted for birth order					
Years of edu	PGS1	9369	−0.007 (−0.011 to −0.002)	−0.002 (−0.008 to 0.004)	0.367 (0.262 to 0.509)
Years of edu	PGS2	6374	−0.006 (−0.010 to −0.001)	−0.002 (−0.007 to 0.005)	0.338 (0.237 to 0.480)
Years of edu	PGS1 + PGS2	6374	−0.006 (−0.010 to −0.001)	−0.002 (−0.008 to 0.005)	0.341 (0.242 to 0.492)

[a] Assuming a heritability of estimated in the rightmost column.
[b] Assuming an α of 3.56 (Gao et al., 2019).

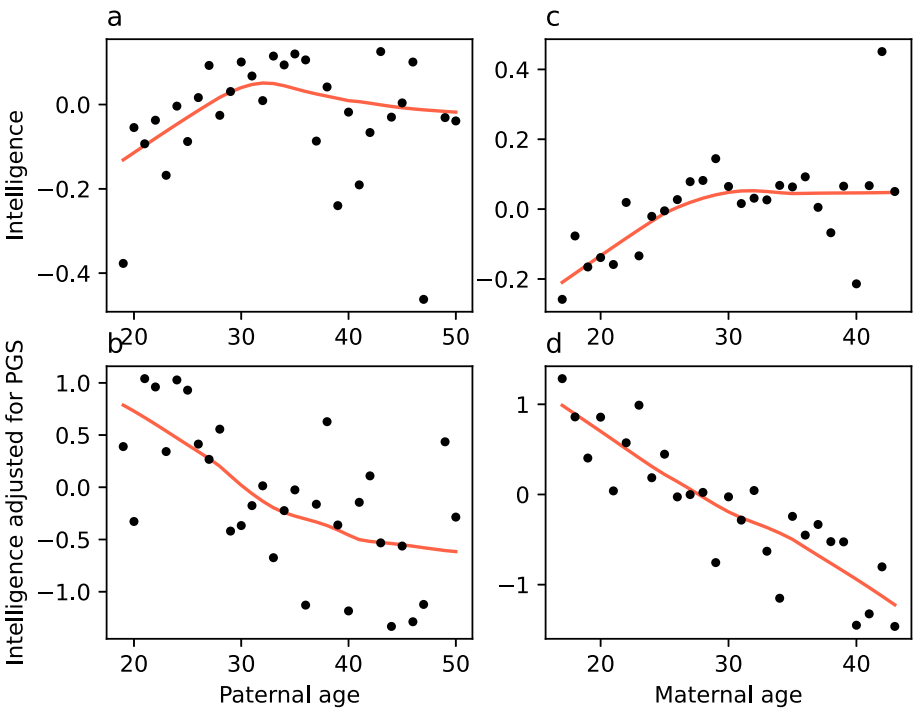

Fig. 2. Parental age and z-score difference in intelligence.
(a, b) Paternal age and intelligence unadjusted for and adjusted for PGS difference. (c, d) Maternal age and intelligence unadjusted for and adjusted for PGS difference.
Lowess fit with default options was applied to the data and was shown as red lines.

maternal ratio of the projected age effects after controlling the genetic effect matches the male-female ratio of mutation rate.

Using PGS that explains only a portion of heritability, I projected the influence of the PGS when it reaches full heritability. As can be seen in Fig. 2, after controlling for PGS, the inverted U-shaped relationships between parental ages and IQ turned monotonically negative, consistent with the expected additive effects of accumulating *de novo* mutations. It supports the idea that the inverted U-shaped relationships were caused by the confounding effect of parental characteristics. The results were replicated using educational attainment from the same dataset and Health and Retirement Study (Figs. S5 and S6). The initially inverted U-shaped or monotonic positive relationship all turned monotonic negative, suggesting the method is robust. After adjustment for gender, birth year, their interaction term, maternal age, and genetic principal components, it gives an estimate of −0.013 (95 % CI, −0.025 to −0.002, N = 4692) SD change per year (or −2.0 IQ points per decade,) rise in paternal age. After further adjustment for birth order, the effect decreased to −0.004 (95 % CI, −0.018 to 0.011, N = 4673) SD change per year (or −0.6 IQ points per decade). It is still in the expected direction, but not showing statistical significance. To estimate the effect of *de novo* mutation accumulation, should birth order be controlled? On one hand, a possible association between birth order and changing *in-utero* environment (*e.g.*, Karmaus, 2001) suggests birth order should be controlled. On the other hand, the negative correlation between fertility and IQ/educational attainment (*e.g.*, Beauchamp, 2016) suggests those with more siblings tend to have lower genetic IQ and, therefore, a lower genetic IQ for people with higher birth order and the adjustment for birth order may attenuate the effect. The real effect may lie somewhere between them.

The most commonly seen explanation of the paternal age effect in literature is *de novo* mutation accumulation. If it is the sole factor behind the estimates, the results would suggest a large accumulative effect since mutations are accumulating throughout the lifetime of both sexes (Gao et al., 2019; Kong et al., 2012). Because mutations are random, the combined effect should follow a normal distribution and would have a substantial contribution to the variance of intelligence of the population. *de novo* mutations in recent generations are rare in the present generation and hence could not be detected in GWAS, and thus creating missing heritability. Assuming an average paternal and maternal age of 30 and 28 and an α of 3.56 (Gao et al., 2019) for calculating the combined paternal and maternal age effect, it would suggest a 7.5-point generational decline in genetic variants underlying intelligence. Even if only an amount equal to the lower estimate can be attributed to mutation accumulation, it would still suggest a 2.4-point generational decline. Intelligence levels had been rising rapidly in the population (*i.e.*, the Flynn effect). In the United States, it has been rising at about 3 IQ points per decade. However, we have witnessed a turning point recently. The average IQ score began to fall in many countries (Dutton et al., 2016). This phenomenon, which refers to a decrease in population IQ score, has been termed the "Lynn effect" by Furnham (2009). In the United States, Platt et al. (2019) have shown a recent decrease for older adolescents though still rising for children. Even before that, some indicators have already indicated a genetic decline of general intelligence for over a century [*i.e.*, the Woodley effect, see Egeland, 2022 for a review]. Bratsberg and Rogeberg (2018) have shown the Lynn effect can be explained by within-family variation in intelligence scores, and conclude that the effect could only reflect environmental factors. If any portion of the estimates here can be attributed to mutation accumulation, it suggests that genetic deterioration is compatible with the within-family variation.

Nonetheless, we should be cautious in the interpretation of the results. The association might not equal the effect of *de novo* mutations because of other mechanisms that can explain the association (Malaspina et al., 2005) and not all kinds of *de novo* mutations are associated with parental age. Consider the following points. (1) Biological. (1.1) Epigenetic effect. It is thought that some age-related epigenetic alterations that escaped reprogramming may be associated with the paternal age effect. This suggests that the association may be epigenetic in origin, and adverse changes may be reset in future generations. However, a recent study compared grandchildren of young and old grandparents and found no age-associated methylation (the most-studied kind of epigenetic mechanism) alterations could transmit trans-generationally (Jenkins et al., 2019). On the other hand, the deleterious effect of microRNA alternations in aged sperm was recently discovered for model animals (*e.g.*, Liang et al., 2022), which is a direction worth looking into. (1.2) Effect of *in-utero* environment. Advanced maternal age is

associated with an increased risk of pregnancy complications (Salem Yaniv et al., 2011); they might be environmental in origin and may play a role in the negative association between maternal age and intelligence. Hence the effect is environmental and would not accumulate through generations and future generations would reverse such negative effects by reproducing earlier. However, in the regression analysis, the age of the other parent has been controlled and the paternal age effect (which constitutes a major proportion of the expected pre-generation decline estimate) is independent of maternal age. (1.3) Effect of structural variants. The rate of *de novo* structural variants is not correlated with parental age (Belyeu et al., 2021) and hence their effect is not considered in the analysis. Despite a much lower frequency of *de novo* structural variants, existing structural variants were shown to be deleterious to cognition (Fitzgerald et al., 2020) and their effects should be assessed in a future analysis. (2) Psychosociological. The rearing environment provided by parents of different ages is another potential source of confounding. Older parents offer more economic, social and cultural resources to children after taken controlling for socioeconomic background and family structure (Powell et al., 2006). Therefore, environmental effects may lower the estimate. (3) Others. (3.1) Noise from adoptees. Participants adopted as a child may have reported the age of their non-biological parents, which could introduce noise to the analysis. According to Census 2000, the proportion of adopted children is small in the United States (Kreider, 2003) and no significant impact on the estimates is expected. (3.2) There might be yet unknown factors confounding the association. Despite such limitations, the present results are still useful because the large influence of parental intelligence was removed.

It is important to distinguish between the effects of environmental factors and mutation accumulation. Environmental effects are reversible after a generation but mutation accumulation would accumulate across generations. Therefore, although the estimated effects are small (especially after controlling for birth order), if they are indeed caused by *de novo* mutations, they can add up to become big effects. This issue is important and deserves further investigation. In the United States, the national prevalence of developmental disabilities has been increasing (Zablotsky et al., 2019). Some of these disorders have a polygenic genetic architecture similar to intelligence. It is an open question whether mutation accumulation plays a role.

The study presents a new way of estimating heritability by calculating how much variance should be controlled when genotype confounding was removed from an effect (*i.e.*, when the paternal-maternal ratio of the projected age effects after controlling the genetic effect matches the male-female ratio of mutation rate). This is fundamentally different from family-based and current SNP-based heritability, which are both based on estimating the phenotypic variance explained by genomic similarities. The heritability of IQ whether unadjusted or adjusted for birth order, was 0.56 (95 % CI, 0.30 to 1.47, N = 4692) and 0.73 (95 % CI, 0.42 to 2.08, N = 4673), respectively. This is close to the 0.60 to 0.80 estimates for adults in traditional family studies (Bouchard, 1998). The heritability estimates of educational attainment (EA) unadjusted for birth order in the Health and Retirement Study were 0.37 (95 % CI, 0.27 to 0.51, N = 9369) and 0.34 (95 % CI, 0.24 to 0.48, N = 6374) using two alternative sets of PGS. This is close to the 0.38 estimate of heritability from twin studies (US studies weighted by the number of participants in Branigan et al. (2013)). In the Wisconsin Longitudinal Study, the heritability of educational attainment unadjusted and adjusted for birth order was higher at 0.49 (95 % CI, 0.32 to 0.90, N = 7248) and 0.59 (95 % CI, 0.33 to 1.43, N = 4602), respectively. For the background and more discussion on the method of heritability estimation, please refer to Appendix.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.paid.2023.112137.

CRediT authorship contribution statement

Mingrui Wang: Conceptualization, Analysis and Writing.

Data availability

The research has used publicly avaliable data.

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Appendix A. Heritability estimation based on parental age effects

The study presents a new way of estimating heritability based on parental age effects. This is an essential part of the analysis since they were used in the parental age effect estimates. Meanwhile, heritability estimation is independent of the main research topic and the background and discussion are presented as follows.

Heritability refers to the proportion of phenotypic variance that can be attributed to genetic factors. It is typically estimated using pedigree-based methods. Let's take height as an example. Suppose the variance in height is genetically determined, then the height should be more similar among relatives than non-relatives, more similar among closer relatives than more distant relatives, and more similar among identical twins than non-identical twins. Suppose the variance in height is environmentally determined, the phenotypic variance would not be more similar among people with higher relatedness. By comparing whether people with higher relatedness are more likely to be taller or shorter, the heritability of height can be estimated. (Note, common environmental influence should be additionally controlled.) This is the idea behind the classical family-based analysis and various methods have been developed (Kaufman, 2009). With the advances in molecular biology, single nucleotide polymorphisms (SNP) have been genotyped and related heritability estimation methods have been developed. Since we share a common ancestor, unrelated individuals are actually distantly related. Genomic relatedness matrix restricted maximum likelihood (GREML) calculates heritability using a similar way to classical family-based analysis and relatedness is calculated from SNP-derived genetic relationship (Yang et al., 2017). For example, if height is heritable, then taller strangers would be more similar genetically as measured by genotyping arrays. Another method called LD score regression (LDSC) has been developed. In GWAS, each SNP was tested for correlation with a trait. LDSC calculates heritability based on whether the distribution chi-square statisticsof SNP-phenotype associations differs from that under the expectation of the null hypothesis (Bulik-Sullivan et al., 2015). Both family-based analysis and GREML are based on estimating the phenotypic variance explained by genomic similarities. LDSC is based on how the distribution of chi-square statistics of the SNP-phenotype associations differs from the null hypothesis, and essentially also on the phenotypic variance explained by genomic similarities.

Here, I propose a new way of estimating heritability. Suppose there is a genotypic confounding to an effect. If we know the de-confounded effect and the genotype value of each individual, in theory, we will be able to confirm the de-confounded effect by controlling for the genotype value of each individual when calculating the effect. However, as discussed in the Introduction section, PGS calculated from GWAS results can only partly explain the heritable influence. Thus, PGS can only partly de-confound the effect. Since the effect would change linearly as the proportion of phenotype explained by PGS increases (as well as the effect when not controlling for PGS), we can project how will the effect change when an even higher proportion were explained. When the projected effect reaches the known de-confounded effect, the proportion of phenotype explained should be the heritability of the trait.

In the present analysis, we don't even know the de-confounded effect.

Nevertheless, since there are two projections (paternal and maternal age effect) and we already know the ratio of paternal and maternal age effect (by assuming it is equal to the ratio of male and female mutation rate), we can solve an equation to get heritability and parental age effects at once.

The heritability estimated in the new way is close to those estimated by the family-based method. The heritability of educational attainment (unadjusted for birth order) estimated from Wisconsin Longitudinal Study is higher than that estimated from the Health and Retirement Study. The difference may have reflected the difference between state-wide and nation-wide samples and show the method being sensitive to known equality × heritability interaction (Heath et al., 1985). However, it could also be the result of random fluctuation. Additional replications should be done.

The new way is based on calculating how much variance should be controlled when genotype confounding was removed from an effect. The method contrasts with existing methods, which are based on how much phenotypic variance can be explained by pedigree. Current SNP-based methods ignore the contribution from rare variants and provide an estimate for the lower bound of heritability. Whereas in the present method, the estimated value should be the full heritability. If validated, the present method would represent a methodological contribution to behaviour genetics. A source of inaccuracy may come from the possibility that other confounding factors exist and, after genotype differences were controlled, the ratio of paternal-maternal effect does not equal the ratio of male-female germline mutation rate. This possibility was discussed in the Discussion section. We can next look for a more certain de-confounded effect to refine the method.

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