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Evaluating the performance of polygenic indices of neuropsychiatric conditions and brain endophenotypes in four UK population samples

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Article

Keywords:

Posted Date: July 30th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10446737/v1

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Additional Declarations: The authors have declared there is **NO** conflict of interest to disclose

Abstract

Neuropsychiatric polygenic indices (NPGIs) are used as genetic predictors of poor mental health. However, NPGIs are also associated with environmental factors which could affect mental health in adulthood, including the rearing environment. Hence, their "genetic" effects are both direct and environmentally mediated. There is a need to identify alternative genetic predictors without environmental signal. Endophenotype-based polygenic indices (EPGIs) trained on brain structure and function are under-studied alternatives which, due to their relative biological proximity, may exhibit associations with mental health outcomes which are less environmentally mediated than those of NPGIs. Using four representative UK samples (*Understanding Society*; UKHLS, NCDS, BCS70 and MCS) we employ sex-stratified path models to estimate the direct and environmentally mediated effects of eleven NPGIs and 30 EPGIs on adult mental health, focussing on the rearing environment. The depression NPGI is consistently associated with mental health symptoms across most sex-stratified sub-samples (best meta-analysis β = 0.091, p 0.001) but demonstrates 1.6–24.5% environmental mediation. Seven other NPGIs and three EPGIs show sample- and sex-specific associations with mental health symptoms. NPGIs for attention deficit hyperactivity disorder, depression and substance use disorder are robustly associated with measures of the rearing environment, which in turn are frequently associated with mental health symptoms. Sensitivity analyses find that NPGI associations vary substantially depending on who is included in the sample. In conclusion, the rearing environment likely mediates a substantial portion of NPGIs' so-called "genetic" effects on mental health symptoms, but EPGIs are not currently powerful enough to replace them.

Introduction

Mental health conditions constitute a substantial individual and societal burden, contributing an estimated 14.6% of years lived with disability globally [1], although this figure may be an underestimation [2]. In England, the prevalence of common mental disorders - such as anxiety and depression - amongst adults has been estimated at one in six [3]. Mental health conditions are multifactorial - the average heritability is estimated at 46% [4], with major depression estimated at around 31–42% [5], hence both genetic and environmental factors play a substantial role in their aetiology. Genetic liability towards a mental health outcome is often measured using polygenic indices (PGIs) a.k.a. polygenic (risk) scores, which are usually trained on neuropsychiatric conditions (neuropsychiatric PGIs; NPGIs). NPGIs have been associated with sub-clinical symptom measures including depressive symptoms [6], thought problems [7] and externalizing behaviour [8], and with intermediate phenotypes (endophenotypes [9]) such as structural [10] and functional [11] brain measures. Efforts to understand how mental health is influenced by the interplay of genetic and environmental factors include a growing literature on gene-environment interaction (GxE) which uses statistical interactions between NPGIs and environmental exposures [12,13]. It is important to use accurate measures of genetic liability in such studies, however NPGIs are unsuitable due to their lack of biological clarity, their dependence on sample characteristics, and the risk that their associations are misinterpreted as evidence for genetic essentialism and determinism [14]. A key argument against such interpretations is the presence of gene-environment correlation (rGE) [15] wherein NPGIs exhibit statistical associations with environmental factors which may in turn have an independent effect on mental health outcomes [16–18]. Hence, NPGIs contain a combination of biological and environmental signal, which could upwardly bias their estimated "genetic" effects on mental health.

Despite this, NPGIs likely index biological processes which are pertinent to mental health. NPGIs are calculated based on genome-wide association studies (GWAS) of neuropsychiatric conditions including neurodevelopmental (e.g. attention deficit hyperactivity disorder; ADHD [19], and autism spectrum disorder; ASD [20]) and mental health (e.g. major depressive disorder; MDD [21], bipolar disorder; BD [22], post-traumatic stress disorder; PTSD [23], eating disorders; ED [24], anxiety disorders; AD [25], schizophrenia; SCZ [26], obsessive-compulsive disorder; OCD [27], and substance use disorders;

SUD [8]) conditions. These GWAS have enhanced our understanding of the genetic contribution to poor mental health, with downstream analyses overwhelmingly implicating brain tissues as mediators of these genetic associations. A recent review [28] highlights the main mediating cell types for SCZ, BD and MDD, specifically glutamatergic neurons which connect cortical and subcortical regions, and GABAergic neurons which connect structures within each of these regions. However, other tissues have been implicated by downstream analyses of neuropsychiatric GWAS: genetic loci linked to the "cross-disorder" factor (resulting from a meta-analysis of eight conditions [29]) and depression [21] are significantly enriched for genes expressed in the pituitary gland and skeletal muscle, respectively. Hence, the biological signal remains heterogeneous and difficult to interpret.

One way to reduce this biological complexity could be to use PGIs based on GWAS of endophenotypes, instead of neuropsychiatric conditions. GWAS have been performed on a range of brain phenotypes including molecular and neuroimaging-based measures, many of which have demonstrated genomic overlap with neuropsychiatric conditions, making them candidate endophenotypes for poor mental health. It is relatively unknown whether endophenotype PGIs (EPGIs) are powerful enough to associate with mental health symptoms in population samples. Nominal associations have been observed between depression remission and PGIs for both caudate volume and protein levels [30,31], and PGIs of AI-derived neuroimaging phenotypes have nominally improved prediction of mental and behavioural disorders [32]. An EPGI which robustly associates with mental health symptoms would be easier to interpret than an NPGI because the former could reasonably be conceived as a proxy for its respective endophenotype, e.g. cerebellar volume or global white matter integrity. Brain endophenotypes have demonstrated lower polygenicity than neuropsychiatric conditions [33,34] supporting the notion that they are less complex and more amenable to genetic characterisation. It remains unknown whether these properties could translate into EPGIs which exhibit less environmental signal than NPGIs.

As mentioned, NPGIs exhibit rGE: statistical associations with environmental exposures from across the life course [16,17,35], including those occurring during childhood and adolescence [18,36,37]. Passive rGE refers to genetic associations with the parentally-influenced rearing environment, as opposed to active and evocative rGE wherein the individual's own behaviour contributes to the observed correlation. The rearing environment includes common experiences such as parental divorce and measures of socioeconomic disadvantage which, while not necessarily harmful, are linked to adult mental health when examined at the population level [38–40]. One reason could be that socioeconomic disadvantage [41], including parental unemployment [42] has been associated with adverse childhood experiences (ACEs), which in turn have been associated with higher odds of adverse mental health outcomes in adulthood [43]. Furthermore, parental divorce is sometimes considered an ACE [44] and has been positively associated with offspring depression in adulthood [45]. Parental marital status and measures of socioeconomic disadvantage during childhood have previously demonstrated statistical associations with offspring NPGIs in UK population samples [18]. Furthermore, some of these associations differed across UK birth cohorts born a few decades apart [18]. Hence, NPGIs are unsuitable measures of "genetic" effects not only because they contain environmental signal, but because such signal likely varies across sociocultural contexts.

Several approaches exist for disentangling the environmental signal in GWAS summary statistics, including genomic structural equation modelling, which allows the summary statistics for one GWAS to be statistically "partialled out" from another. Marees et al used this technique to remove the influence of socioeconomic position from the "heritability" (variance explained by genetic factors) of behavioural and neuropsychiatric traits, finding a substantial attenuation for ADHD and smoking behaviours [46]. Another approach is within-family GWAS, whereby modelling kinship during GWAS has been shown to substantially attenuate the heritability of behavioural traits such as household income, while increasing it for biological traits such as asthma [47]. Alternatively, path models can be used to estimate the direct and mediated effects of a PGI on an outcome via the environment, as demonstrated in youth samples for both educational

achievement [48] and more recently for mental health [49]. These studies estimated environmental mediation of 40% and up to 27.5%, respectively, for the effects of PGIs on these outcomes. These findings are all consistent with the notion that PGIs indexing behavioural and neuropsychiatric phenotypes contain environmental signal which could upwardly bias "genetic" associations with mental health outcomes.

To assess the performance of NPGIs and EPGIs, we use path models to estimate the direct and environmentally-mediated effects of eleven NPGIs and thirty EPGIs on adult mental health symptoms in four representative UK population samples. Effect size is estimated using random effects meta-analysis. Environmental mediation is estimated using three rearing environment exposures available in all four samples: whether the participant lived with both parents (family intact), whether the father was employed (father employed) and whether the mother completed secondary education (mother educated). To examine rGE in the data, we report each exposure's associations with PGIs. An extensive set of sensitivity analyses is performed to examine the impacts of inclusion criteria, measurement (of PGIs, mother's education, and mental health symptoms), covariate adjustment, model specification and age at symptom measurement. We hypothesise that NPGIs will exhibit greater environmental mediation and rGE than EPGIs, that environmental mediation and rGE will differ across samples, and that the representativeness of each sample will impact the number and direction of associations observed.

Methods

Samples

Understanding Society (the UK Household Longitudinal Study; UKHLS) was established in 2009 and comprises around 100 000 participants from 40 000 households. The annual main survey collects data from adult participants (16+) on a range of topics. A nurse visit conducted during waves 2 and 3 (2010–2012) yielded genetic data for around 9 900 participants. We perform separate analyses on two sub-samples: the British Household Panel Survey (BHPS) which began in 1991 and was absorbed into UKHLS in 2009, and the General Population Sample (GPS) which began in 2009. BHPS had likely undergone substantial non-random attrition over approximately two decades prior to the nurse visit, while GPS was relatively newly-recruited.

The 1958 National Child Development Study (NCDS) contains over 17 000 individuals born in the same week in 1958. The biomedical survey was carried out at age 44, with over 6 300 participants providing genotype data. The 1970 British Cohort Study (BCS70) contains around 17 000 individuals born in the same week in 1970. The biomedical survey was carried out at age 46, with over 5 500 participants providing genotype data. There is a non-negligible amount of missing childhood data, such that a 2004 technical report found greater non-response in BCS70 compared to NCDS [50]. The Millennium Cohort Study (MCS) contains almost 19 000 individuals born between 2000–2002. The study design includes over-sampling of Black and Minority Ethnic participants [51]. Saliva samples were collected for genotyping from over 7 500 participants when they were aged 14, along with over 12 000 parents.

Survey measures

"Family intact", "father employed" and "mother educated" were binarized based on available data relating to childhood and adolescence. Family intact was based on variables indicating who was living with, or caring for, the respondent. Father employed was based on variables indicating the participants' father's labour market status, occupation, or financial contribution to the household. Mother educated was based on variables which indicate the participant's mother's completion of secondary education, or age of school completion. Full details can be found in the Supplementary Methods, including Supplementary Tables 1–4.

Psychological distress was taken from the earliest adult (16+) survey available, except for BCS70 which had substantial missingness at age 16. For UKHLS, wave 2 was used. For the birth cohorts, distress was measured between age 17–26. UKHLS used the 12-item General Health Questionnaire (GHQ-12) [52], NCDS and BCS70 used the 24-item Malaise inventory [53] (which captures psychological distress and somatic symptoms [54]) and MCS used the 6-item Kessler scale [55]. Outcomes were scaled and centered. Full details in Supplementary Table 5.

Genotype data QC

Quality control (QC) was performed prior to this study (see Supplementary Tables 6 and 7). To ensure harmonisation, we carried out further QC using PLINK2 following the steps outlined in Coleman et al [56]. Individuals were excluded if they were third-degree relatives (or closer), of non-European ancestry (except in MCS), from families with multiple mothers and fathers, had > 1% missingness, or high heterozygosity. Variants were removed if they were duplicated, lacking rsIDs, had > 1% missing data, failed Hardy-Weinberg equilibrium testing (p 0.00001) or had minor allele frequencies (MAF) of < 1%. To maximise similarity of PGI calculation, only the remaining 3 673 101 variants common to all datasets were retained. MCS was then restricted to European participants for main analyses. The MCS dataset with all ancestries was used for sensitivity analyses and will hereafter be referred to as MCS-full. Full details can be found in the supplementary methods.

PGI selection

Summary statistics for AD, ADHD, ASD, BD, cross-disorder, ED, MDD, OCD, PTSD, SCZ and SUD were downloaded from the Psychiatric Genomics Consortium website https://pgc.unc.edu/for-researchers/download-results/ [accessed 7th June 2024] and used to derive NPGIs.

Endophenotype selection was based on a convenient, semi-systematic approach (Supplementary Fig. 1). We focussed on GWAS of human brain endophenotypes, with “brain” in the title, whose results were uploaded to NHGRI-EBI GWAS catalog [57]. Authors must have demonstrated significant genomic overlap between the endophenotype and a mental health-related behavioural outcome. Thirty endophenotypes (regional brain volumes, white matter microstructure, cerebrovascular lesions, resting-state brain activity, and longitudinal change in brain structure) from seven publications [58–64] were included (Supplementary Table 10). For detail, see Supplementary Methods.

Generating PGIs

PGIs were generated using PRSice (v 2.3.5) [65] using the clumping and thresholding approach [66] with six GWAS p-value thresholds (P_ts). PGIs were scaled and centered prior to analysis. The MCS-full PGIs contained more variants than the European-only datasets. See Supplementary Methods and Supplementary Table 11 for details.

Statistical analyses

All analyses were performed using R (v 4.4.0) in RStudio (v 2024.04.2 build 764). All were sex-stratified due to known sex differences in rates and pathophysiological mechanisms of mental health conditions [67,68], environmental risk factors [69–71], and neuroimaging measures of brain structure and function [68,72–74] including with respect to mental health [75]. Complete case analysis was used. Due to partial collinearity between “family intact” and “father employed” resulting from participants whose father passed away, participants were excluded from the main analysis if either

parent was deceased (for brevity, such participants are hereafter referred to as “bereaved”). UKHLS was split into GPS and BHPS sub-samples prior to analysis.

Pearson’s correlation was used to examine collinearity amongst PGIs and ancestry PCs.

Linear regression was used to estimate “total genetic effects” of each PGI (symptoms ~ PGI), and the independent associations of all three exposures (symptoms ~ family intact + father employed + mother educated). Coefficients can be interpreted as betas. The *sem* function from the *lavaan* package (v 0.6–18) was used to run path models. A direct path from PGI to mental health symptoms was used to estimate “direct genetic effects”. To model “indirect genetic effects”, paths from PGI to each of the three exposures were included, along with paths from each of the three exposures to mental health symptoms. The robust weighted least squares estimator was used, and the exposures treated as ordered variables. Coefficients were standardized, making them comparable with the regression betas. For GPS and BHPS, all linear regressions and paths from the PGI to another variable were adjusted for age and age^2.

Coefficients and p values from the “direct genetic effects” paths were used to determine which PGIs were significantly associated with psychological distress. Environmental mediation was estimated using the formula *100 * ((total – direct) / total)* and will hereafter be referred to as “per cent mediated”. To minimise unstable estimates, this was only calculated where at least one of the associations (regression or path model) was at least nominally significant ($p < 0.05$). Positive estimates suggest environmental mediation while values of 0 or below are interpreted as total lack of mediation, i.e. direct genetic effects. To examine rGE, coefficients from paths between PGIs and exposures were also examined.

All PGI analyses were run once per combination of PGI phenotype, P_t, sex, and sample, i.e. 41 * 6 * 2 * 5, respectively. To correct for multiple testing, Bonferroni adjustment [76] was used with a numerator (alpha) of 0.05 and a denominator of 41 (number of phenotypes) i.e. 0.05/41 or 0.00122. This relatively lenient denominator was chosen due to substantial collinearity between the PGIs across P_ts and phenotypes (see Fig. 2 and supplementary Fig. 2), and the relative stringency of the Bonferroni approach.

Meta-analyses were performed on the direct path estimates to obtain an overall estimate of PGIs’ associations with psychological distress. We used the *rma.mv* function from the *metafor* package (v 4.8-0) with a t distribution and restricted maximum likelihood estimation. As the datasets are heterogeneous in terms of age distributions and sociocultural contexts, “dataset” was modelled as a random effect.

Sensitivity analyses

Sensitivity analyses were performed to examine the impacts of inclusion criteria, operationalisation (of PGIs, mother’s education, and symptom scale used), covariate adjustment, model specification and age at symptom measurement. For full details, see Supplementary Methods and Supplementary Table 12.

Results

Descriptive Statistics

Sample size ranged from n = 682 to n = 2 962. MCS had the lowest rates of father employed and family intact, and the highest rates of mother educated. See Table 1. For samples used in sensitivity analyses, see Supplementary Tables 13–16.

Table 1
Descriptive statistics for the main analytical sample.

	GPS		BHPS		NCDS		BCS70		MCS	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
n (%)	2 216 (42.8)	2 962 (57.2)	682 (43.7)	877 (56.3)	2 401 (49.4)	2 460 (50.6)	1 035 (43.3)	1 355 (56.7)	2 026 (48.4)	2 163 (51.6)
Year of birth (age at biospecimen collection for MCS): Mean (SD) range	1956 (16.0) 1917–1994	1958 (15.6) 1915–1994	1954 (14.2) 1913–1986	1954 (14.8) 1914–1987	1958	1958	1970	1970	13.7 (0.5) 13–15	13.8 (0.5) 13–15
Family intact (%)	86.9	85.1	89.0	88.1	85.0	82.3	82.1	83.1	64.3	63.5
Father employed (%)	94.3	92.2	96.9	95.1	91.4	89.7	91.3	89.4	81.4	81.7
Mother educated (%)	47.2	49.6	46.5	41.4	30.0	29.2	54.3	53.1	97.3	97.2

PGI correlations

In the combined UKHLS sample, we examined pairwise correlations between PGIs (P_t 1.0 only) and ancestry PCs. PC 1 is correlated with five NPGIs: SCZ (0.38), BD (0.22), cross-disorder (0.17), MDD (0.13) and ED (-0.13) and five EPGIs: total grey matter volume (GM) (-0.13) and four corpus callosum microstructure traits (-0.16 to 0.15). PC 3 is correlated with ASD (-0.11), brainstem volume (-0.10) and fornix/stria terminalis fractional anisotropy (FXST FA) (0.12). See Fig. 1 and Supplementary Fig. 2 for correlation heatmaps.

Exposure associations with psychological distress

Mutually-adjusted linear regressions show that each exposure was protective ($p < 0.05$) in multiple sex-stratified samples (Supplementary Fig. 3). For path model results and sensitivity analysis results, see Supplementary Fig. 4 and Supplementary Tables 17–23.

PGI associations with psychological distress

In the main analyses, eleven PGIs were significantly associated with psychological distress: eight NPGIs (AD, ADHD, ASD, cross-disorder, MDD, OCD, PTSD and SUD) and three EPGIs (left rostral middle frontal volume (LRostMidFront), GM and total brain volume (TBV)). See Fig. 2. MDD NPGI was the most consistent PGI, showing a positive association in eight of ten sex-stratified samples, excluding men in BHPS and BCS70. For MDD NPGI, the total variance explained in psychological distress was small (see Supplementary Table 24), ranging from 2.4–6.4% for all explanatory variables combined. In linear regressions, estimates were lower (1.6–4.3%) and, for the PGI alone, lower still (0.8% to 2.0%). See Fig. 3 for scatter plot.

In meta-analyses, only two P_ts survived Bonferroni correction, both for MDD NPGI in women ($\beta = 0.089–0.091$, both $p = 0.001$; Supplementary Fig. 5). There was no evidence of heterogeneity (both $p > 0.67$). See Supplementary Table 25 for all meta-analysis results.

The PGI with the second-most consistent associations with psychological distress was ADHD NPGI, mostly showing positive associations in women. Other associations were specific to one sex-stratified sample. Of the EPGIs, one was associated in men (LRostMidFront in GPS and BHPS, with opposite signs) and two in women (GM and TBV in GPS).

As EPGIs only exhibited associations in the age-representative samples (as opposed to those where symptoms were measured between ages 17–26), we ran *post hoc* linear regressions stratified by generation to examine whether associations were driven by the older participants. TBV EPGI exhibits a suggestive negative association with psychological distress in GPS men aged 46–66 at the time of symptom measurement (p 0.01). Unlike in the four oldest strata, the coefficient for LRostMidFront in the youngest stratum of BHPS men is concordant with that of GPS men, however the association is non-significant. For full results, see Supplementary Table 26.

Some of the main analyses' less robust associations were replicated in at least one sex in sensitivity analyses (Supplementary Figs. 6–11). Focussing on EPGIs, the LRostMidFront EPGI was associated with psychological distress in BCS70 men at age 16, GM EPGI in MCS-full women and TBV EPGI in NCDS men at age 50. When MCS was subset to participants whose parents both provided genetic data, all associations between PGIs and mental health were lost. MDD NPGI tended to remain associated with malaise across mid-adulthood, whereas ADHD NPGI did not.

Environmental mediation of PGI associations with psychological distress

The extent of environmental mediation was estimated for PGIs with at least nominal associations with psychological distress. The two most robustly associated NPGIs, MDD and ADHD, consistently showed environmental mediation (1.6–24.5%, and 6.8–49.7%, respectively). All associations were mediated for SUD (7.4–51.6%), and all were direct for OCD (-12.1 - -5.4%). Focussing on significant associations, those of ASD, GM and PTSD PGIs were consistently mediated, and those of cross-disorder and TBV PGIs were consistently direct. See Fig. 4 and Supplementary Table 27. For sensitivity analyses, see Supplementary Figs. 12–17. Mediation estimates were mostly attenuated by modelling pairwise correlation terms between the exposures, and with increasing age for NCDS and BCS70.

Gene-environment correlation

For NPGIs, associations were generally negative such that increased genetic risk was associated with lower chance of family intact, father employed or mother educated. ADHD NPGI was associated with all three exposures, MDD NPGI with two (family intact and father employed) and SUD NPGI with two (family intact and mother educated). Sex differences were observed for several rGE associations, such that associations were significant for one sex but not the other in the same dataset. See Fig. 5 for main analysis results and Supplementary Figs. 18–34 for supplementary analyses.

For family intact, the sample with the highest number of associations was MCS, while none were observed in BCS70. For father employed, again the sample with the highest number of associations was MCS, while none were observed in BHPS. For mother educated, the highest number of associations was observed in NCDS, with no associations in MCS or GPS.

Sensitivity analyses

Inclusion criteria made substantial differences to rGE. In MCS, the trios sub-sample exhibited almost no rGE, while including all ancestries substantially increased rGE. When bereaved participants were included, father employed became associated with SUD NPGI in NCDS men and MCS women.

Including vocational qualifications in mother's education generally increased its rGE in BCS70. When age adjustment was omitted in GPS, family intact became associated with ADHD NPGI in women, consistent with the main analysis results for MCS and NCDS. Looking across time points in NCDS and BCS70, rGE was generally similar at multiple ages.

Discussion

In this study, we examined whether endophenotype-based polygenic indices (EPGIs) could be used as measures of genetic risk for poor mental health, by comparing their performance to those trained on neuropsychiatric conditions (NPGIs). Compared to NPGIs, EPGIs are arguably more interpretable because they index biologically proximal phenotypes such as brain structure and function. However, their ability to robustly associate with psychological distress, without exhibiting mediation via the rearing environment, was unknown. Using path models in four representative UK population studies, we demonstrate that neither NPGIs nor EPGIs exhibit associations with psychological distress that are both robust and un-mediated.

We hypothesised that NPGIs would exhibit greater environmental mediation and rGE than EPGIs, but this was not clearly demonstrated. For five NPGIs and one EPGI, all significant associations with psychological distress were mediated, while all were direct for two NPGIs and one EPGI. Furthermore, some PGIs were modestly collinear with ancestry PCs, suggesting some shared signal with geographical location [77]. Hence, environmental signal is widespread across most PGIs and is not confined to one category (neuropsychiatric vs endophenotype). The largest estimated magnitudes of mediation were, however, observed in NPGIs.

We also hypothesised that environmental mediation and rGE would differ across samples with differing sociocultural contexts. This was clearly demonstrated to be the rule rather than the exception. Samples generally showed more rGE where rates of exposures were lower, i.e. family intact and father employed in MCS, and mother educated in NCDS and BCS70. Sensitivity analyses also demonstrated that including participants of all ancestries, and excluding participants without parental DNA available, had a substantial impact on rGE. The latter drastically increased the exposure rates, and removed almost all of the PGIs' associations with exposures and outcomes. Hence, genetic studies which rely on trio samples may produce severely biased results. It is unclear whether the additional rGE observed in MCS-full was driven by differences in LD structure which impacted the operationalisation of PGIs. In another sensitivity analysis, the inclusion of participants who had lost a parent during youth led to associations between father employed and the SUD NPGI in two samples. Hence, rGE is highly dependent on who is included in the analytical sample.

Our final hypothesis was that sample representativeness would impact the number and direction of associations observed. The lack of association between MDD NPGI and psychological distress in BHPS men and BCS70 men could be underpinned by various forms of non-participation. When biospecimens were collected in BHPS, approximately two decades had elapsed since initial study recruitment. Since this was an age-representative sample, loss-to-follow-up could have impacted the representativeness of BHPS to a greater extent than the birth cohorts, as older participants could have passed away during that time. BCS70 has a relatively high amount of missing data [50] which, if not missing at random, could have impacted representativeness. Furthermore, male sex has been associated with non-participation [78,79]. Hence, these two sex-stratified samples are likely less representative than the eight others. Furthermore, a lack of representativeness could explain the opposite sign of association between LRostMidFront EPGI and psychological distress in BHPS men compared to GPS men. Additionally, there were several unusual results in BHPS and BCS70 regardless of sex, and in men regardless of sample. For the former, ADHD NPGI was associated with women's psychological distress in all samples except, which in turn exhibited several unique rGE associations with EPGIs. Regarding sex differences, father employed was not associated with psychological distress in men, potentially due to collider bias as socioeconomic disadvantage is associated with non-participation [78,79]. Furthermore, despite there being no theoretical basis for observing sex differences in the rearing environment or in rGE, these were observed. This

could arise due to sex-specific participation bias, which has previously been observed in genetic datasets [80]. It may be possible to overcome the effects of limited representativeness by using weights, which have been shown to de-bias estimates of downstream analyses when used in GWAS [81], and which could also be applied to studies which use PGIs. This could be examined in future research.

To the best of our knowledge, this was the first study to examine whether a range of EPGIs were associated with psychological distress in four adult UK population samples. Looking across main analyses, sensitivity analyses and *post hoc* generation-stratified analyses, our results suggest that some EPGIs could be useful measures of genetic risk of poor mental health. The total brain volume (TBV) EPGI was protective against psychological distress in GPS women, and in middle-aged men in two samples (NCDS at age 50, and nominally in a middle-aged stratum of GPS). This pattern of association could suggest that higher genetically-estimated TBV is protective against poor mental health, but only in women and middle-aged men. This is plausible considering that, phenotypically, total brain volume is smaller in women compared to men [82] and shows steeper decline over time in men compared to women [83]. Smaller total brain volume has been associated with worse mental health symptoms across the life course, i.e. in both preadolescents [84] and in a middle-aged and elderly sample [85]. The fact that associations between TBV EPGI and psychological distress were consistently un-mediated makes this a promising candidate which warrants examination in future studies.

In the main analyses, the LRostMidFront and GM EPGIs were negatively associated with psychological distress in men and women in GPS, respectively. Both showed a replication in one other sample of the same sex in sensitivity analyses. While the direction of association for LRostMidFront EPGI was inverted in BHPS compared to GPS, this could be due to reduced representativeness of the former as discussed. Besides, the trend was concordant with GPS in the small number of millennials in BHPS, and the finding was replicated in BCS70 men at age 16. Phenotypically, the gyrification of this region is lower in men compared to women [86,87]. Its cortical thickness has been linked to MDD incidence and duration [88], and its volume and cortical thickness have been linked to stress-related phenotypes in men, specifically PTSD [89] and salivary cortisol [90], respectively. The association of GM EPGI in GPS women was replicated in MCS-full women. This sex-specific association is plausible given that total GM volume is, on average, lower in women compared to men [82]. Total GM volume has been phenotypically associated with mental health symptoms in preadolescents [91] and with depression symptoms and status in clinical cohorts [92]. Taken together, this suggests that LRostMidFront and GM EPGIs warrant further investigation as measures of genetic risk for poor mental health.

It is worth noting that the aetiology of neuropsychiatric conditions is far too complicated [93] to be satisfactorily explained by combining PGIs and measures of the rearing environment in a regression-based analysis. In the present study, explained variance in psychological distress was estimated at a maximum of just 6.4% for the combination of PGI, age and three measures of the rearing environment. We have demonstrated how, when examined at the population level, genetic factors, parental behaviours and psychological distress exhibit very weak correlations, which vary across sociocultural contexts, and which therefore do not determine one another.

Limitations

There are several limitations in the present study. Firstly, we used fairly simple models. In the main analyses, we did not adjust for ancestry PCs, however doing so in GPS made little difference. Furthermore, we focussed on passive rGE and didn't model evocative or active rGE. Participants' own relational and occupational functioning – which likely has an impact on psychological distress – likely exhibits associations with several PGIs. Future research could model a greater number of covariates and mediators.

Secondly, the exposures were binary, which may not be sufficiently nuanced. For example, “father employed” does not fully capture the level of socioeconomic advantage in the household, nor does it distinguish between unemployment and estrangement. Furthermore, measures were often based on a single point in time. However, MDD NPGI has exhibited a significant association with a five-level measure of parental socioeconomic position in MCS, along with nominal associations with finance issues and father’s involvement in upbringing [18]. In the present study we showed similar patterns of rGE in the same sample using binary exposures, hence, these may be reasonable proxies for more granular and pertinent measures.

Thirdly, our outcomes were limited to cross-sectional, continuous measures of psychological distress. Further research could focus on other outcomes such as the chronicity of symptoms, or health service use.

Fourthly, while we consider EPGIs to be more interpretable than NPGIs, it is important to acknowledge their limitations. The endophenotypes measured in their respective GWAS were likely influenced by a range of factors besides genetics, including environmental exposures and stochastic variation. Direction of causality between such endophenotypes and mental health outcomes can only be established with longitudinal neuroimaging studies.

Finally, our main analyses focussed on adult participants of European ancestry. Including participants of non-European ancestry had a substantial impact on rGE, however, we did not ascertain the reasons for this, which could include increased sample size and the greater number of genetic variants included in the PGIs in this sample. Furthermore, we could not examine the impact of including older participants of different ancestries. Finally, inferences cannot be made beyond the UK context. Future research should examine a wide range of populations from across the world, including all ages and ancestries.

Conclusion

In conclusion, this study demonstrates that neuropsychiatric polygenic indices contain environmental signal. The two key lines of evidence supporting this are the fact that direct genetic effects were usually smaller than total genetic effects, and the observed correlations between NPGIs and the rearing environment, which in turn vary according to sample characteristics. Hence, NPGI associations with mental health outcomes cannot be interpreted as purely “genetic”. In seeking to identify an endophenotype-based alternative to NPGIs, we demonstrate that some brain volume-based PGIs show associations with psychological distress in a minority of sex-stratified sub-samples with different age distributions. These inconsistent associations could result from true between-group heterogeneity in the biological underpinnings of psychological distress, or may be due to under-powered neuroimaging GWAS. Future work should focus on EPGIs based on larger GWAS, and should include a broader range of target populations, with greater variation in sociocultural context, age and ancestry.

Declarations

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

A.D. is supported by the ESRC (ES/T00200X/1, project reference number 2765580). L.S. is supported by MR/W004984/1. M.K. is supported by the University of Essex, ESRC (RES-596-28-0001) and ESRC (ES/S012486/1; ES/Y003071/1). J.M. is supported by ES/Y003071/1. The funders had no involvement in the analysis or preparation of the paper.

We would like to thank the study participants who gave their time and biological samples to support population research. We acknowledge the use of the High Performance Computing Facility (Ceres) and its associated support services at the University of Essex in this work. We are grateful for the technical advice from Tim Morris, Liam Wright, Alexander Hatoum and Grace Lutter.

Author contributions

A.D. designed the project, conducted the analyses and drafted the manuscript. L.S. was the principal supervisor and M.K. was the secondary supervisor. All authors provided feedback on the manuscript.

Data availability

Information on how to access the data can be found on the *Understanding Society* website https://www.understandingsociety.ac.uk/documentation/health-assessment/accessing-data/ and on the Centre for Longitudinal Studies website https://cls.ucl.ac.uk/data-access-training/genetic-data-and-biological-samples/.

Code availability

The code is available at https://github.com/AnnaDearman/endophenotype-polygenic-indices/.

Supplementary information is available at MP's website

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Figures

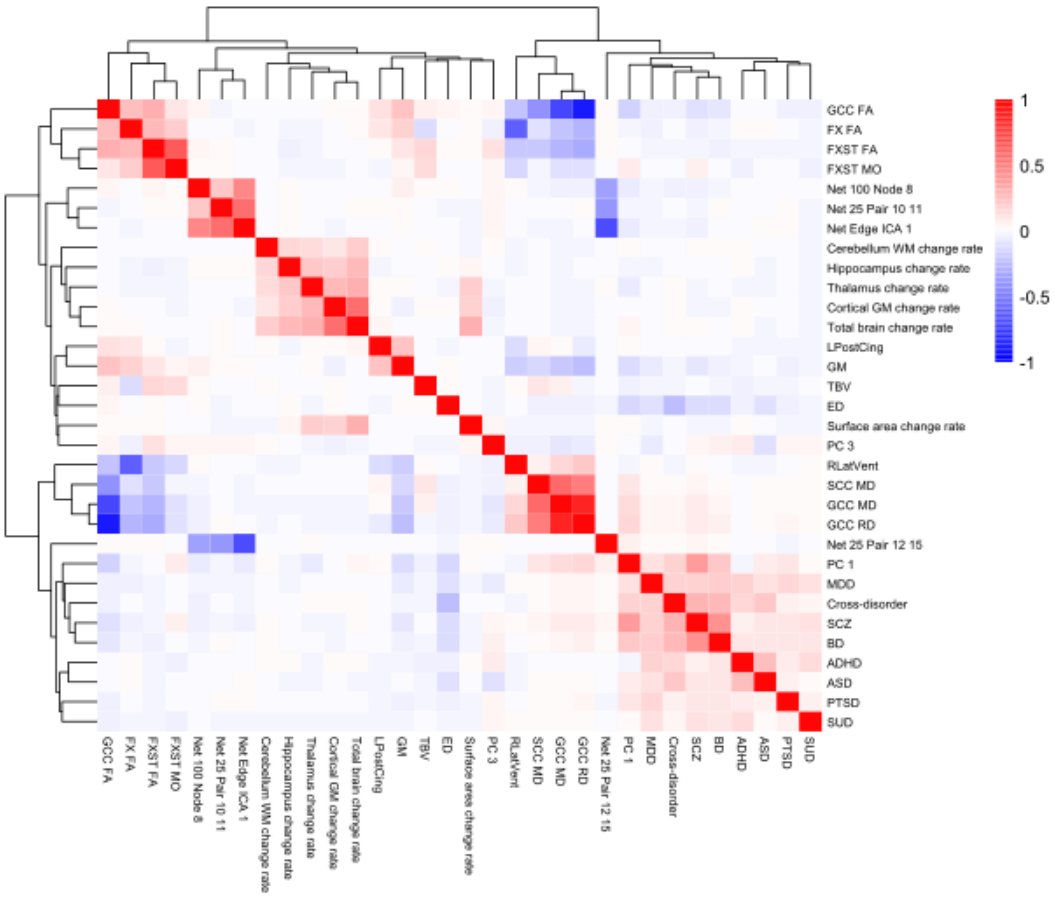


Figure 1

Correlation heatmap of PGIs and ancestry PCs in UKHLS (GPS and BHPS). For readability, plot is restricted to PGIs and PCs with at least four absolute correlations greater than 0.1, and to P_t 1.0. ADHD = attention deficit hyperactivity disorder, ASD = autism spectrum disorder, BD = bipolar disorder, ED = eating disorder, FA = fractional anisotropy, FXST = fornix/stria terminalis, GCC = genu of corpus callosum, GM = grey matter volume, ICA = independent components analysis, LPostCing = left posterior cingulate, MD = mean diffusivity, MDD = major depressive disorder, MO = mode of anisotropy, PC = principal component (of ancestry), PTSD = post-traumatic stress disorder, RLatVent = right lateral ventricle, SCC = splenium of corpus callosum, SCZ = schizophrenia, SUD = substance use disorders, TBV = total brain volume, WM = white matter.

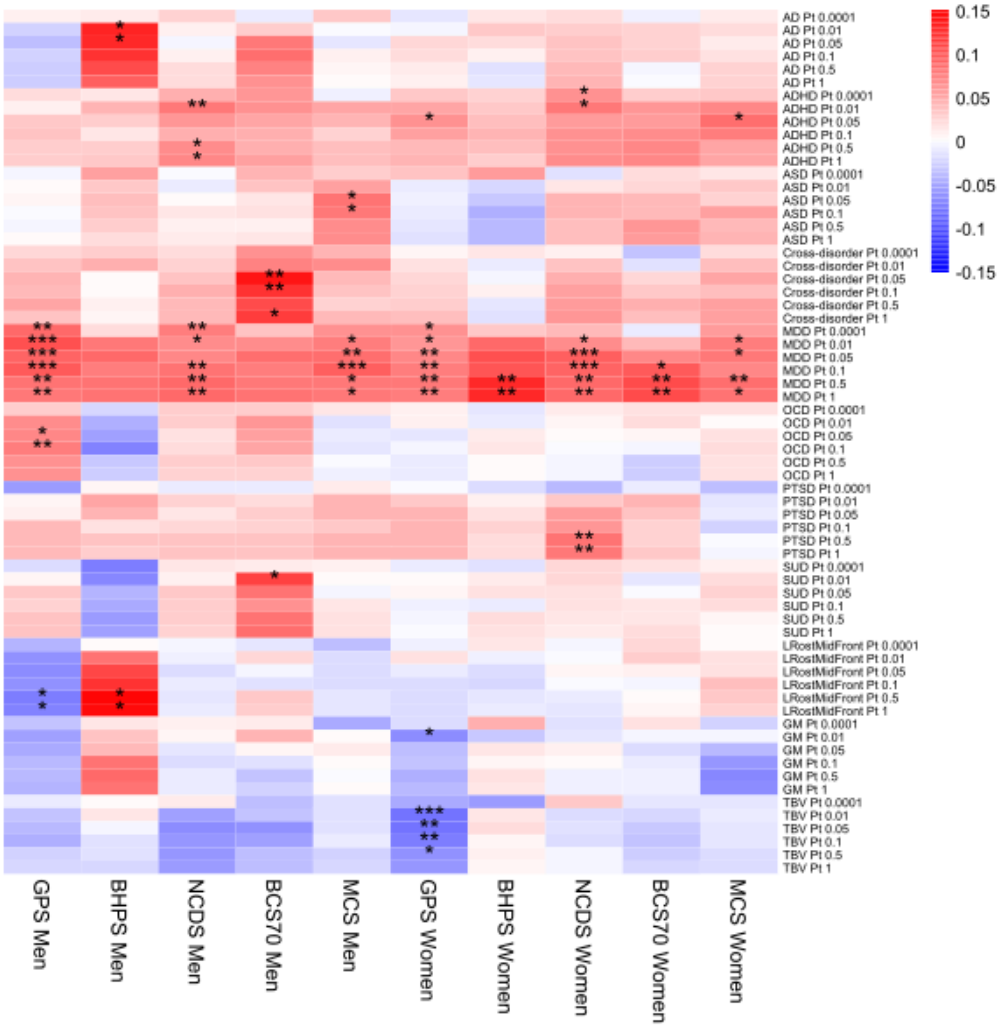


Figure 2

Associations between PGIs and mental health symptoms. * = p < 0.05/41, ** = p < 0.01/41, *** = p < 0.001/41. AD = anxiety disorders, ADHD = attention deficit hyperactivity disorder, ASD = autism spectrum disorder, BCS70 = the 1970 British Cohort Study, BHPS = British Household Panel Survey, GM = total grey matter volume, GPS = general population sample of Understanding Society, LRostMidFront = left rostral middle frontal region volume, MCS = Millennium Cohort Study, MDD = major depressive disorder, NCDS = the 1958 National Child Development Study, OCD = obsessive-compulsive disorder, Pt = p value threshold, PTSD = post-traumatic stress disorder, SUD = substance use disorders, TBV = total brain volume.

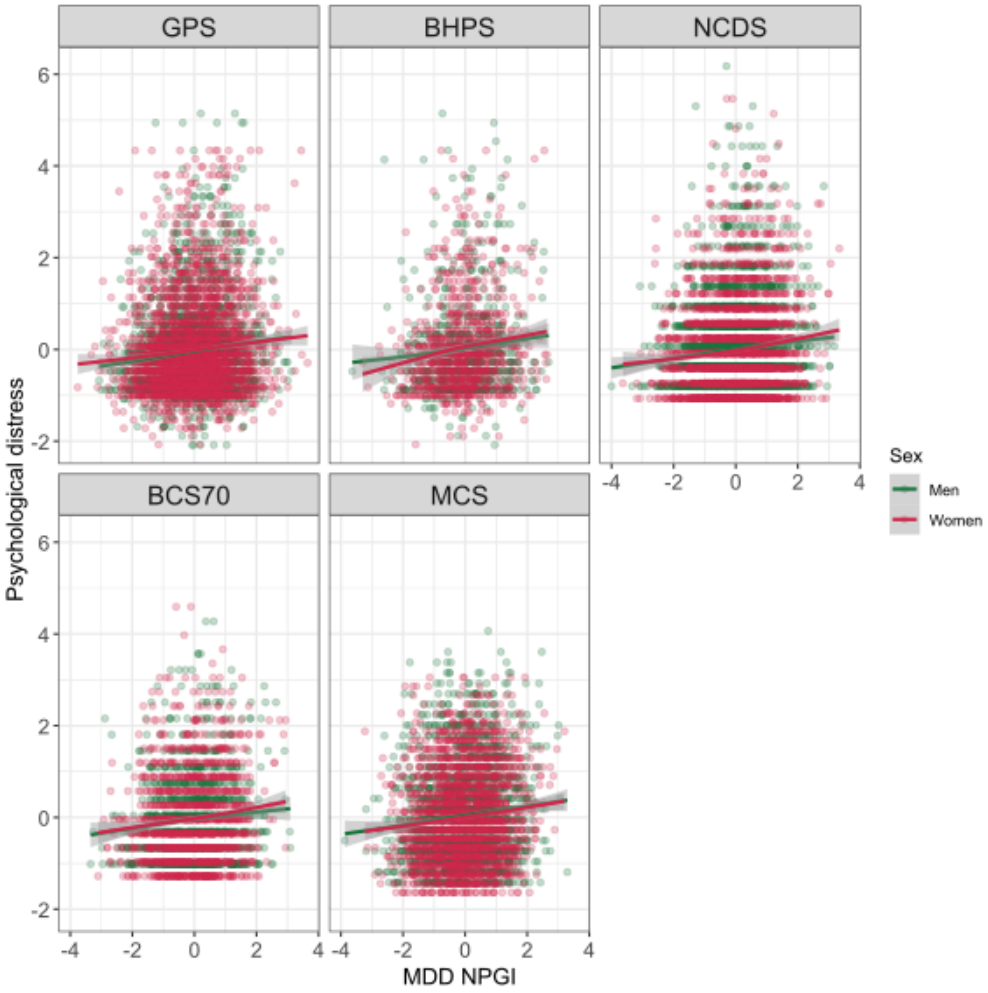


Figure 3

Bivariate correlation between psychological distress and MDD NPGI, using the optimal P_t per sex-stratified sample (optimal P_t = 0.01 for GPS men, 0.05 for BHPS men, NCDS women and BCS70 men, 0.1 for MCS men, 0.5 for GPS women and MCS women, and 1.0 for BHPS women, NCDS men and BCS70 women). BCS70 = the 1970 British Cohort Study, BHPS = British Household Panel Survey, GPS = general population sample of Understanding Society, MCS = Millennium Cohort Study, MDD = major depressive disorder, NCDS = the 1958 National Child Development Study, NPGI = neuropsychiatric polygenic index, P_t = p value threshold.

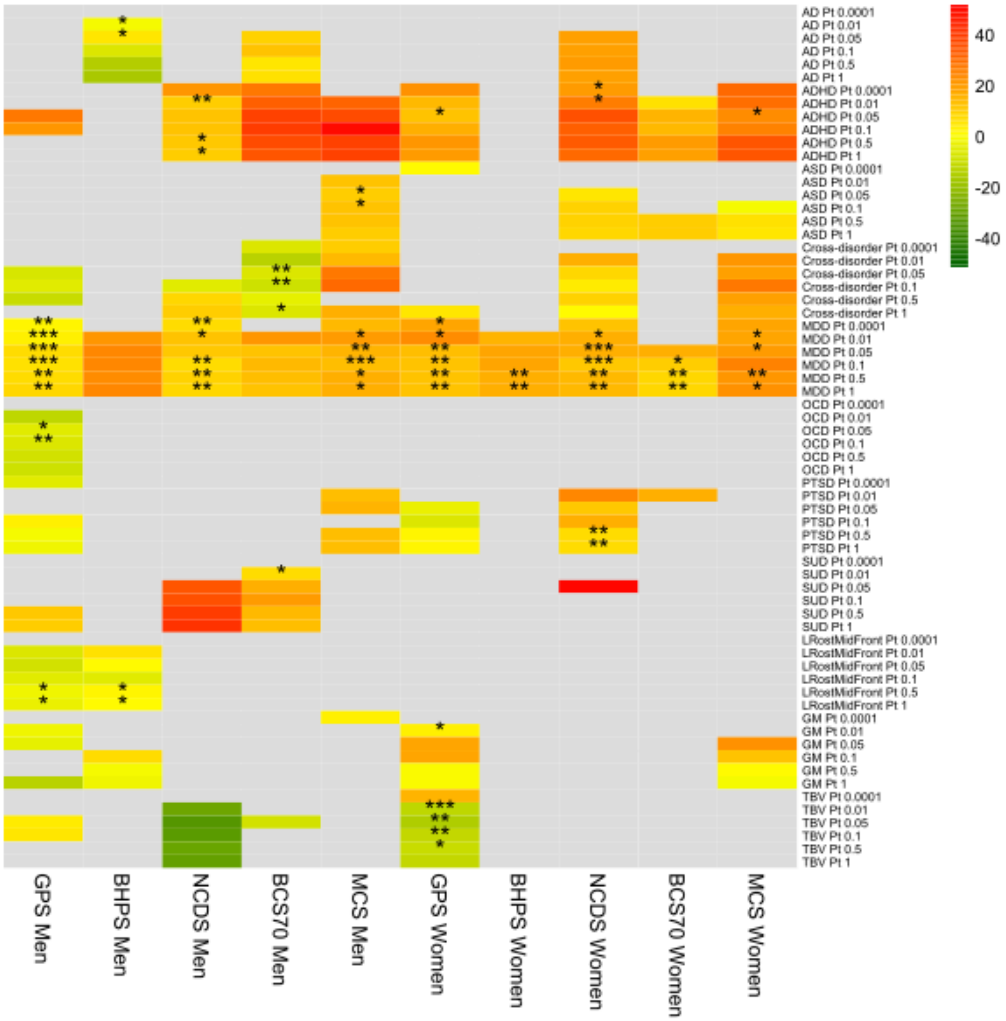


Figure 4

Estimates of “per cent mediated”, i.e. the extent to which polygenic index (PGI) associations with psychological distress are mediated by the rearing environment. Values of 0 and below represent no environmental mediation while positive values indicate some environmental mediation. Values were not calculated when the linear regression (for estimating total genetic effects) and the path model (for estimating direct genetic effects) both had p values greater than 0.05. * = $p < 0.05/41$, ** = $p < 0.01/41$, *** = $p < 0.001/41$. AD = anxiety disorders, ADHD = attention deficit hyperactivity disorder, ASD = autism spectrum disorder, BCS70 = the 1970 British Cohort Study, BHPS = British Household Panel Survey, GM = total grey matter volume, GPS = general population sample of Understanding Society, LRostMidFront = left rostral middle frontal region volume, MCS = Millennium Cohort Study, MDD = major depressive disorder, NCDS = the 1958 National Child Development Study, OCD = obsessive-compulsive disorder, Pt = p value threshold, PTSD = post-traumatic stress disorder, SUD = substance use disorders, TBV = total brain volume.

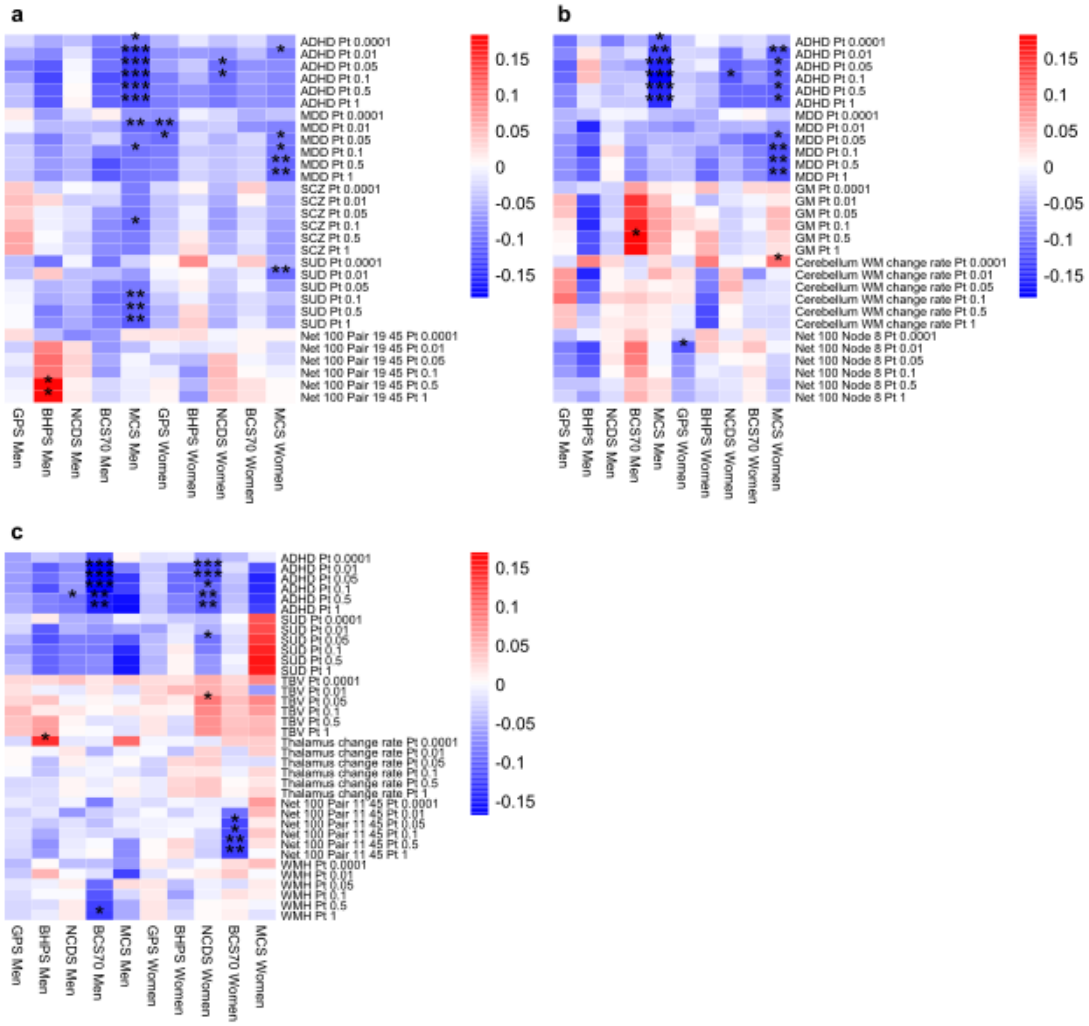


Figure 5

Associations between polygenic indices (PGIs) and exposures from the rearing environment. * = p < 0.05/41, ** = p < 0.01/41, *** = p < 0.001/41. a. family intact, b. father employed, c. mother educated. ADHD = attention deficit hyperactivity disorder, BCS70 = the 1970 British Cohort Study, BHPS = British Household Panel Survey, GM = grey matter, GPS = general population sample of Understanding Society, MCS = Millennium Cohort Study, MDD = major depressive disorder, NCDS = the 1958 National Child Development Study, Pt = p value threshold, SCZ = schizophrenia, SUD = substance use disorders, TBV = total brain volume, WM = white matter, WMH = white matter hyperintensities.

Supplementary Files

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