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Genetic Susceptibility to Neurodevelopmental Conditions Is Associated With Neonatal DNA Methylation Patterns in the General Population: An Individual Participant Data Meta-Analysis

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ABSTRACT

BACKGROUND: Autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and schizophrenia (SCZ) are highly heritable and linked to disruptions in fetal neurodevelopment. Epigenetic processes, such as DNA methylation (DNAm), are considered a key pathway of interest. However, it is unclear whether 1) genetic susceptibility to neurodevelopmental conditions (NDCs) is associated with DNAm patterns already at birth, 2) DNAm patterns are unique or shared across conditions, and 3) neonatal DNAm patterns can be leveraged to enhance genetic prediction of neurodevelopmental outcomes.

METHODS: We conducted epigenome-wide meta-analyses of genetic susceptibility to ASD, ADHD, and SCZ (measured with polygenic scores [PGSs]) and cord blood DNAm in 4 European population–based cohorts (n_{pooled} = 5802; 50.2% female). We estimated DNAm pattern overlap between PGSs using heterogeneity statistics. Furthermore, we built methylation profile scores for each PGS to test incremental variance explained over genetic data alone in 130 developmental outcomes from birth to 14 years.

RESULTS: In probe-level analyses, the SCZ PGS was associated with neonatal DNAm at 246 loci ($p < 9 \times 10^{-8}$), predominantly in the major histocompatibility complex, supporting an early-origins perspective on SCZ. Functional characterization confirmed strong genetic effects, blood-brain concordance, and enrichment for immune-related pathways. Eight loci were identified for the ASD PGS (mapping to *FDFT1* and *MFHAS1*) and none for the ADHD PGS. Differentially methylated regions were detected across PGSs (130–166 regions). Overall, DNAm signals were largely distinct between conditions. Incorporating neonatal DNAm data in genetic prediction models nominally increased the explained variance for several cognitive and motor outcomes.

CONCLUSIONS: Genetic susceptibility to NDCs, particularly SCZ, is detectable in cord blood DNAm in the general population.

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Neurodevelopmental conditions (NDCs) are complex, multifactorial conditions involving perturbations in brain development that begin during fetal life (1). The corresponding DSM-5 diagnostic category includes conditions with a developmental onset, such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) (2). Schizophrenia (SCZ) is also regarded as having neurodevelopmental origins despite its later onset (1,3). A common feature of these conditions is their high genetic contribution, as evidenced by family-based studies (twin-based heritability estimates ~80%) (4–6) and by large-scale genome-wide association studies (GWASs) (single nucleotide polymorphism [SNP]–based heritability ~20%–40%) (7). However, the mechanisms underlying phenotypic presentation of these conditions remain poorly understood. Epigenetic processes that modulate gene expression, such as DNA methylation (DNAm), may be promising molecular candidates as biological markers and mediators of genetic and environmental influences on neurodevelopmental risk.

DNAm from peripheral blood is increasingly being used in clinical genetics to diagnose Mendelian NDCs (e.g., Kabuki syndrome), showing utility in differentiating complex cases with ambiguous presentation compared with genetic data alone (8). In contrast, the extent to which genetic susceptibility

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to complex (polygenic) NDCs is associated with DNAm is less clear. A limited set of studies has examined whether GWAS-derived polygenic scores (PGSs) for ASD, ADHD, and SCZ are associated with DNAm patterns, irrespective of diagnosis (all case-control, $n < 1300$) (9–11). Using an ASD PGS, Hannon *et al.* identified genome-wide associations with DNAm from neonatal heel pricks at 2 CpGs (9). Mooney *et al.* (10) found that an ADHD PGS was associated with saliva-derived DNAm in mid-to-late childhood at 1 CpG. Finally, a SCZ PGS was associated with adult blood DNAm at 2 CpGs, but those findings were not replicated in an independent cohort (11). For ASD and ADHD, DNAm patterns were more strongly associated with the PGSs than with diagnoses (9,10).

While these studies provide preliminary support for a link between genetic susceptibility to NDCs and DNAm, key gaps remain. First, studies have focused exclusively on clinical case-control samples (9–11), and associations in the general population remain uncharacterized. This is important given the dimensional nature of NDCs, with a diagnosis of ADHD, ASD, or SCZ representing the tail end of the continuum. Furthermore, DNAm patterns are developmentally dynamic and tissue specific (12), and existing studies have varied in the age and tissue of DNAm assessment (i.e., neonatal heel pricks, saliva in childhood, blood in adulthood). Growing evidence suggests that DNAm variation at birth may be a particularly informative marker of NDCs, with several recent studies identifying cord blood DNAm as a stronger predictor of neurodevelopmental risk than DNAm measured during childhood. Potentially, cord blood DNAm represents a better proxy for congenital effects associated with NDCs, with this signal becoming noisier over time [e.g., due to postnatal exposures and immune-related changes (12)]. The fact that cord blood DNAm also precedes symptom onset makes it an especially promising tissue for early risk prediction while minimizing reverse causality. Second, studies have focused on PGSs for individual NDCs in isolation when investigating associations with DNAm despite evidence of their genetic and phenotypic overlap (7). Examining multiple PGSs within the same individuals would offer a valuable opportunity to characterize unique versus shared epigenetic correlates of genetic susceptibility across conditions. Finally, no research has examined the potential utility of PGS-associated epigenetic marks in predicting (neuro)developmental outcomes. Given that PGSs explain little variance in NDCs in the general pediatric population, examining whether incorporating additional information on genetic susceptibility from another regulatory level amplifies PGS prediction could have important implications for early risk detection (13).

To address these gaps, we conducted a large-scale epigenome-wide association meta-analysis of genetic susceptibility to ASD (ASD PGS), ADHD (ADHD PGS), and SCZ (SCZ PGS), leveraging individual participant data from 4 population-based prospective cohorts with DNAm obtained in the same tissue and at the same time point (cord blood at birth), with a total combined sample size of 5802 participants from Northern European datasets. Specifically, we 1) investigated epigenome-wide associations of PGSs with cord blood DNAm in the general population (probe and region level) and performed follow-up characterization to examine genetic influences (i.e., methylation quantitative trait loci [mQTL] and twin heritability estimates), associations with gene expression, blood-brain concordance, enrichment for correlated regions of systemic interindividual variation (CoRSIVs) and functional pathways, and developmental dynamics of identified signals; 2) examined whether epigenetic patterns are distinct or shared across genetic susceptibilities; and 3) explored whether incorporating a DNAm-based measure of genetic susceptibility at birth amplifies PGS prediction of neurodevelopmental outcomes across childhood (see Figure 1 for graphical abstract).

METHODS AND MATERIALS

Study Population

This study features 4 North European population–based birth cohorts: the Generation R Study (GenR) (14), the PREDO (Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction) study (15), the ALSPAC (Avon Longitudinal Study of Parents and Children) (16), and the MoBa (Norwegian Mother, Father, and Child Cohort Study) (17). Inclusion criteria and cohort-specific descriptions of methods can be found in the Supplement. Final meta-analyses included 5802 participants (Table 1). This study was conducted according to the Helsinki Declaration of the World Medical Association, and written informed consent was provided by all participating mothers.

Genetic Susceptibility for NDCs

We calculated PGSs with the latest GWAS summary statistics for 3 NDCs: ASD (ASD PGS), ADHD (ADHD PGS), and SCZ (SCZ PGS) (18–20) using *PRSice2* (default settings) (21). First, we clumped correlated SNPs within a 250-kb window at an R^2 threshold of 0.1. Second, PGSs were thresholded by calculating PGSs against multiple *p*-value thresholds (only SNPs with a GWAS *p* value below threshold were included in the PGS) and selecting the threshold for which each PGS explains the most variance in diagnosis-related measures across cohorts (0.5 for the ASD PGS and 0.01 for the ADHD PGS). For the SCZ PGS, we used a fixed threshold ($p < .05$), consistent with the original GWAS (18), due to the lack of SCZ measures in most cohorts. Detailed descriptions of genotyping and PGS calculation are available in the Supplement.

DNA Methylation

DNAm was extracted from cord blood and bisulfite-converted with the EZ-96 DNA Methylation kit (Zymo Research Corporation). Samples were run on the Illumina Infinium HumanMethylation450 BeadChip (450K) or MethylationEPIC BeadChip (EPIC), which include 485,577 and 867,531 CpGs, respectively. DNAm beta values were winsorized ($>$ median $\pm$ 3 IQR) to reduce the influence of outliers. We excluded sites only available in one cohort and sites that are cross-reactive or polymorphic (indicated by the R package *maxprobes*; https://github.com/markgene/maxprobes), leaving 795,580 sites (380,778 EPIC only; $n = 2504$ [43.5%] run on EPIC). Cohort-specific quality control and normalization procedures are described in the Supplement.

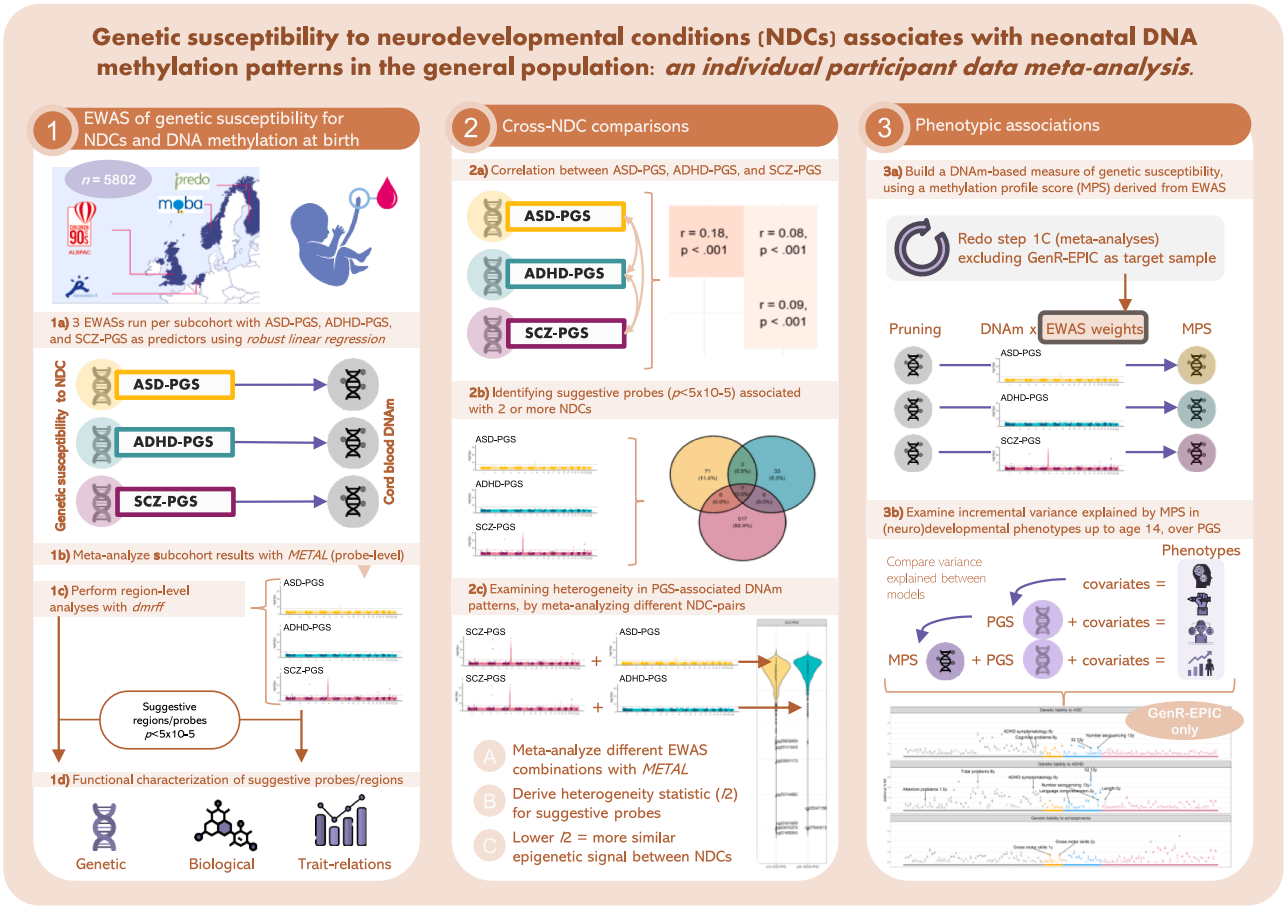

Figure 1. Graphical abstract. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DNAm, DNA methylation; EWAS, epigenome-wide association study; MoBa, Norwegian Mother, Father, and Child Cohort Study; MPS, methylation profile score; NDC, neurodevelopmental condition; PGS, polygenic score; PREDO, Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction; SCZ, schizophrenia.

Covariates

Covariates included sex, gestational age at birth, and prenatal maternal smoking assessed by DNAm (for comparability across cohorts); cell-type proportions estimated via the combined cord blood reference panel (22); genomic principal components to adjust for population stratification; and technical covariates (e.g., sample plate) to adjust for batch effects (differing per cohort) (for full details, see the Supplement).

Analyses

Step 1: Epigenome-Wide Associations. In each cohort, a probe-level epigenome-wide association study (EWAS) was performed to assess associations between PGSs and DNAm at birth with covariate adjustment, separately for each PGS and CpG. We ran robust linear regression analyses, which are less sensitive to potential heteroscedasticity and influential outliers, using the *MASS* R package. Findings from individual cohorts were pooled with inverse-variance weighted fixed effects meta-analysis with *METAL* [EWAS-MA (23)]. To assess the stability of probe-level results, a leave-one-out meta-analysis was performed for the top 10 significant hits per PGS. In addition, we performed regional analyses examining differentially methylated regions (DMRs) with the *dmrff* R package (24) based on the same association models used in the probe-level EWAS analyses (PGS as predictor, DNAm as outcome, adjusted for covariates). DMRs were defined by grouping CpGs no more than 500 base pairs apart, with a nominal $p < .05$ for the association with the phenotype and consistent direction of effect, following the default settings of the *dmrff* package. In both probe-level and regional analyses, associations were defined as genome-wide significant at a threshold of $p < 9 \times 10^{-8}$ (Bonferroni-corrected for the number of effective tests) (25) and suggestive at $p < 5 \times 10^{-5}$. Suggestive results were functionally characterized using publicly available resources (Table 2). Enrichment was tested against background (450K only due to the availability of resources) using Fisher's exact test, where significance was deemed nominal at $p < .05$.

Step 2: Cross-NDC Comparisons. First, we examined correlations across PGSs. Second, we identified CpGs shared across the PGS-specific EWAS-MA results, defined as CpGs showing suggestive associations with >2 PGSs. Third, we pooled pairwise EWAS-MA results with inverse-variance weighted fixed effects meta-analysis (cross-NDC meta-analyses) in *METAL*. We examined heterogeneity (I^2) statistics

Table 1. Population Characteristics for Each Subcohort

Characteristic	$GenR_{450K}$	$GenR_{EPIC}$	PREDO	ALSPAC	MoBa-1	MoBa-2	MoBa-4	MoBa-8
Cohort Characteristics								
Cohort	GenR	GenR	PREDO	ALSPAC	MoBa	MoBa	MoBa	MoBa
Country	NL	NL	FI	UK	NO	NO	NO	NO
Sample size	1317	1097	767	731	355	128	739	668
DNAm array for cord blood	450K	EPIC	450K	450K	450K	450K	EPIC	EPIC
Child Characteristics								
Child sex, female	657 (49.1%)	568 (51.8%)	362 (47.2%)	372 (50.9%)	169 (47.5%)	70 (53.9%)	362 (51.3%)	353 (54.6%)
Gestational age at birth, weeks	40.1 ± 1.5	40.0 ± 1.5	39.8 ± 1.6	39.6 ± 1.5	39.6 ± 1.5	39.4 ± 1.5	39.6 ± 1.7	39.6 ± 1.9
Maternal Characteristics								
Age, years	31.7 ± 4.2	31.4 ± 4.3	33.3 ± 5.8	29.8 ± 4.5	–	–	–	–
Self-reported smoking during pregnancy, yes	275 (23.0%)	227 (22.9%)	31 (4.0%)	75 (10.3%)	40 (11.2%)	12 (10.9%)	55 (9.6%)	67 (12.2%)
Educational level, low	24 (1.8%)	45 (4.2%)	335 (43.7%)	109 (15.1%)	6 (1.8%)	4 (3.3%)	12 (1.8%)	8 (1.3%)
Educational level, medium	426 (32.8%)	377 (35.3%)	173 (22.6%)	457 (63.3%)	133 (33.3%)	33 (27.3%)	225 (33.4%)	199 (32.3%)
Educational level, high	848 (65.3%)	645 (60.4%)	239 (31.2%)	156 (21.6%)	220 (64.9%)	84 (69.4%)	437 (64.8%)	410 (66.5%)

Values are presented as *n* (%) or mean ± SD. Missing data for maternal characteristic variables resulted in percentages that do not total 100%. Self-reported smoking is shown here as more directly interpretable than prenatal maternal smoking as assessed by DNAm. Rates of low/medium/high education are not directly comparable across cohorts because educational systems differ between countries. See the Supplement for specific definitions. 450K indicates the Illumina Infinium HumanMethylation450 BeadChip. EPIC indicates the Illumina MethylationEPIC BeadChip.

ALSPAC, Avon Longitudinal Study of Parents and Children; DNAm, DNA methylation; FI, Finland; GenR, Generation R; MoBa, Norwegian Mother, Father, and Child Cohort Study; NL, the Netherlands; NO, Norway; PREDO, Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction; UK, United Kingdom.

for suggestive sites, which quantifies the proportion of variance across PGS-specific EWAS-MA results attributable to heterogeneity rather than chance. Lower I^2 values indicate that epigenetic associations across the compared PGSs are more similar. Significance was defined as nominal at $p < .05$.

Step 3: Phenotypic Associations. Finally, we built a DNAm-based measure of genetic susceptibility by constructing methylation profile scores (MPSs) for each PGS at birth. These MPSs capture the broader epigenetic signal associated with genetic susceptibility for ASD, ADHD, and SCZ, offering a more comprehensive representation of underlying patterns than single-probe analyses alone (26). We assessed whether these MPSs explain additional variance in (neuro)developmental outcomes beyond the PGSs. To avoid overfitting, we reran the EWAS-MAs after removing one dataset, which we used as a target sample ($GenR_{EPIC}$, $n = 1097$). We multiplied the EWAS-MA weights for suggestive sites ($p < 5 \times 10^{-5}$) with methylation beta values in $GenR_{EPIC}$, performed clumping based on co-methylation patterns within $GenR_{EPIC}$, and aggregated weighted sites into a single score, similar to PGS calculation. As a baseline, we examined the incremental variance explained by PGS, above covariates, in (neuro)developmental phenotypes. Next, we evaluated incremental variance explained by the MPS above the PGS and covariates. Significance was defined phenotype-wide as $p < 8 \times 10^{-4}$ [Bonferroni-corrected for the number of effective tests $n = 61$, Galwey method (27)] and nominally at $p < .05$.

Further details about steps 1 to 3 are provided in the Supplement.

RESULTS

Study Characteristics

A total of 5802 participants (50.2% female) were included in this study (Table 1). Gestational age at birth was similar across cohorts; however, rates of self-reported pregnancy smoking (any) ranged from 9.6% in MoBa-4 to 23.0% in GenR.

Epigenome-Wide Associations of Genetic Susceptibility for NDCs and DNAm at Birth

In probe-level analyses, the ASD PGS was associated with DNAm at 8 CpGs at birth after Bonferroni correction ($p < 9 \times 10^{-8}$; in total 74 suggestive at $p < 5 \times 10^{-5}$), all of which were located on chromosome 8 close to the *MFHAS1* and *FDFT1* genes (Table S1) and several suggestive sites present only on the EPIC array (55%). No probe-level hits were identified for the ADHD PGS after Bonferroni correction (36 suggestive, 42% EPIC only) (Table S2). In contrast, the SCZ PGS was associated with DNAm at 246 CpGs after Bonferroni correction (517 suggestive, 12% EPIC only) (Table S3). Many of these sites were on chromosome 6 (96% at $p < 9 \times 10^{-8}$, 87% suggestive), mostly within the major histocompatibility complex (MHC) (between positions 29,640,000 and 33,120,000; 62% at $p < 9 \times 10^{-8}$, 61% suggestive). EWAS-MA results showed no indication of genomic inflation (Figure 2), leave-one-out results indicated that associations were unlikely to be driven by a single cohort (Figure S1), and within-condition heterogeneity was low (ADHD PGS and ASD PGS) to moderate (SCZ PGS) (Supplemental Results).

We further explored the role of the MHC region in the $GenR_{EPIC}$ sample, which provides the largest sample size with the most recent and more complete EPIC array data. We revisited the SCZ PGS EWAS, introducing 2 new SCZ PGSs that omit SNPs within the MHC locus (chr6:25,000,000–35,000,000). For the first PGS (PGS SCZ_{Rank1}), we excluded the MHC region (chr6:25,000,000–35,000,000) while preserving the broader surrounding area of rs115329265 (chr6:28,303,247–28,712,247). For the second PGS (PGS $SCZ_{Variant}$), we excluded the MHC region (chr6:25,000,000–35,000,000) while preserving

Table 2. Functional Characterization of Probe-Level and Region-Level Suggestive Sites, $p < 5 \times 10^{-5}$

	Probe Level			Region Level		
	ASD PGS, 74 Suggestive Sites, 55% EPIC Only	ADHD PGS, 36 Suggestive Sites, 42% EPIC Only	SCZ PGS, 517 Suggestive Sites, 12% EPIC Only	ASD PGS, 251 Regions Including 1335 Suggestive Sites, 4.6% EPIC Only	ADHD PGS, 305 Regions Including 1635 Suggestive Sites, 5.6% EPIC Only	SCZ PGS, 297 Regions Including 1564 Suggestive Sites, 5.6% EPIC Only
Blood mQTL through the GoDMC database (http://www.godmc.org.uk/)	24 sites (73%), significantly more than background, $p = .001$	11 sites (52%), not significant, $p = .270$	379 sites (83%), significantly more than background, $p = 3.0 \times 10^{-69}$	689 sites (54%), significantly more than background, $p = 8.6 \times 10^{-10}$	870 sites (56%), significantly more than background, $p = 3.0 \times 10^{-8}$	976 sites (66%), not significant, $p = .082$
Average Twin Heritability Estimates (http://www.epigenomicslab.com/online-data-resources)	30% [range 0–86%], significantly more than background, $p = .016$	38% [range 0–89%], significantly more than background, $p = .006$	51% [range 0–99%], significantly more than background, $p = 1.3 \times 10^{-72}$	24% [range 0–99%], significantly more than background, $p = 5.5 \times 10^{-26}$	24% [range 0–98%], significantly more than background, $p = 2.6 \times 10^{-32}$	19% [range 0–99%], significantly more than background, $p = 1.5 \times 10^{-8}$
HELIX Web Catalog: to test whether the identified top hits are associated with gene expression changes in blood by eQTM mapping (https://helixomics.isglobal.org/)	7 sites (21%), significantly more than background, $p = .001$	4 sites (19%), significantly more than background, $p = .016$	203 sites (45%), significantly more than background, $p = 6.2 \times 10^{-140}$	112 sites (9%), significantly more than background, $p = 1.4 \times 10^{-9}$	137 sites (9%), significantly more than background, $p = 8.7 \times 10^{-12}$	84 sites (6%), not significant, $p = .099$
Average Blood-Brain Correlation: to probe cross-tissue correspondence of the identified sites (BECon) (https://redgar598.shinyapps.io/BECon/)	0.04 [range −0.45 to 0.56]	0.01 [range −0.52 to 0.30]	0.11 [range −0.56 to 0.85]	0.01 [range −0.47 to 0.71]	−0.01 [range −0.62 to 0.75]	−0.02 [range −0.61 to 0.74]
MissMethyl Package: to identify enrichment for broader molecular pathways and functions (GO Collection) (for the full list, see Tables S12–S14)	No enrichment	No enrichment	166 pathways, mainly adaptive immune system; 45 when restricted to epigenome-wide significant hits, $p < 9 \times 10^{-8}$	No enrichment	No enrichment	No enrichment
Number of CoRSIVs: these regions are intercorrelated over long genomic distances and conserved across ancestry and tissue because they were established before cell-type differentiation, especially sensitive to periconception environment (28)	1 site (3%), not significantly more than background, $p = .087$	No enrichment	29 sites (6%), significantly exceeding background, $p = 8.9 \times 10^{-30}$; it is noteworthy that CoRSIVs constitute only 0.4% of the background sites	14 sites (<1%), significantly more than background, $p = 1.8 \times 10^{-5}$	9 sites (<1%), significantly more than background, $p = .044$	9 sites (<1%), significantly more than background, $p = .024$

Table 2. Continued

	Probe Level			Region Level		
	ASD PGS, 74 Suggestive Sites, 55% EPIC Only	ADHD PGS, 36 Suggestive Sites, 42% EPIC Only	SCZ PGS, 517 Suggestive Sites, 12% EPIC Only	ASD PGS, 251 Regions Including 1335 Suggestive Sites, 4.6% EPIC Only	ADHD PGS, 305 Regions Including 1635 Suggestive Sites, 5.6% EPIC Only	SCZ PGS, 297 Regions Including 1564 Suggestive Sites, 5.6% EPIC Only
EpiDelta Tool: characterizes longitudinal epigenetic changes over the first 2 decades of life (http://epidelta.mrcieu.ac.uk/), checked for 1) increase or decrease in methylation across childhood, 2) nonlinearity of change, or 3) differences in interindividual variability	No significant differences	No significant differences	Compared with background, significantly more nonlinear changes in DNAm across childhood, $p = 1.0 \times 10^{-34}$	Compared with background, significantly more 1) increase/decrease in methylation across childhood, $p = 1.6 \times 10^{-11}$	Compared with background, significantly more 1) increase/decrease in methylation across childhood, $p = 2.6 \times 10^{-10}$, 2) nonlinear changes, $p = 3.1 \times 10^{-10}$, and 3) intraindividual differences, $p = .040$	Compared with background, significantly more 1) increase/decrease in methylation across childhood, $p = 2.3 \times 10^{-12}$ and 2) nonlinear changes, $p = .007$
EWAS Catalog: to see whether hits were identified in association with other phenotypes in previous EWASs (44). (Here only notable traits are listed; for the full list, see Tables S15 and S16)	Health conditions, protein levels, ADHD, smoking, alcohol consumption	Health conditions, protein levels	Health conditions, protein levels, several psychiatric conditions (e.g., SCZ, ADHD, and depression), neurocognitive conditions (e.g., mild cognitive impairment and Alzheimer's disease), and adversities (e.g., child abuse)	Several psychiatric conditions (e.g., SCZ, psychosis, substance abuse), neurocognitive conditions, and adversities (e.g., child abuse)	Several psychiatric conditions (e.g., SCZ, psychosis, aggressive behavior, depression, substance abuse), neurocognitive conditions, and adversities (e.g., child abuse)	Several psychiatric conditions (e.g., SCZ, psychosis, aggressive behavior, depression, substance abuse, ADHD), neurocognitive conditions, and adversities (e.g., child abuse)

We note that all these tools, except missMethyl, are only available for probes on the 450K array. Functional enrichment for suggestive probes was compared with background CpGs (array-wide DNAm, only 450K) using Fisher's exact test (nominally significant at $p < .05$). More extensive information on functional characterization is available in Tables S1–S3. EPIC indicates the Illumina MethylationEPIC BeadChip.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CoRSIV, correlated region of systemic interindividual variation; DNAm, DNA methylation; eQTM, expression quantitative trait methylation; EWAS, epigenome-wide association study; GO, gene ontology; mQTL, methylation quantitative trait loci; PGS, polygenic score; SCZ, schizophrenia.

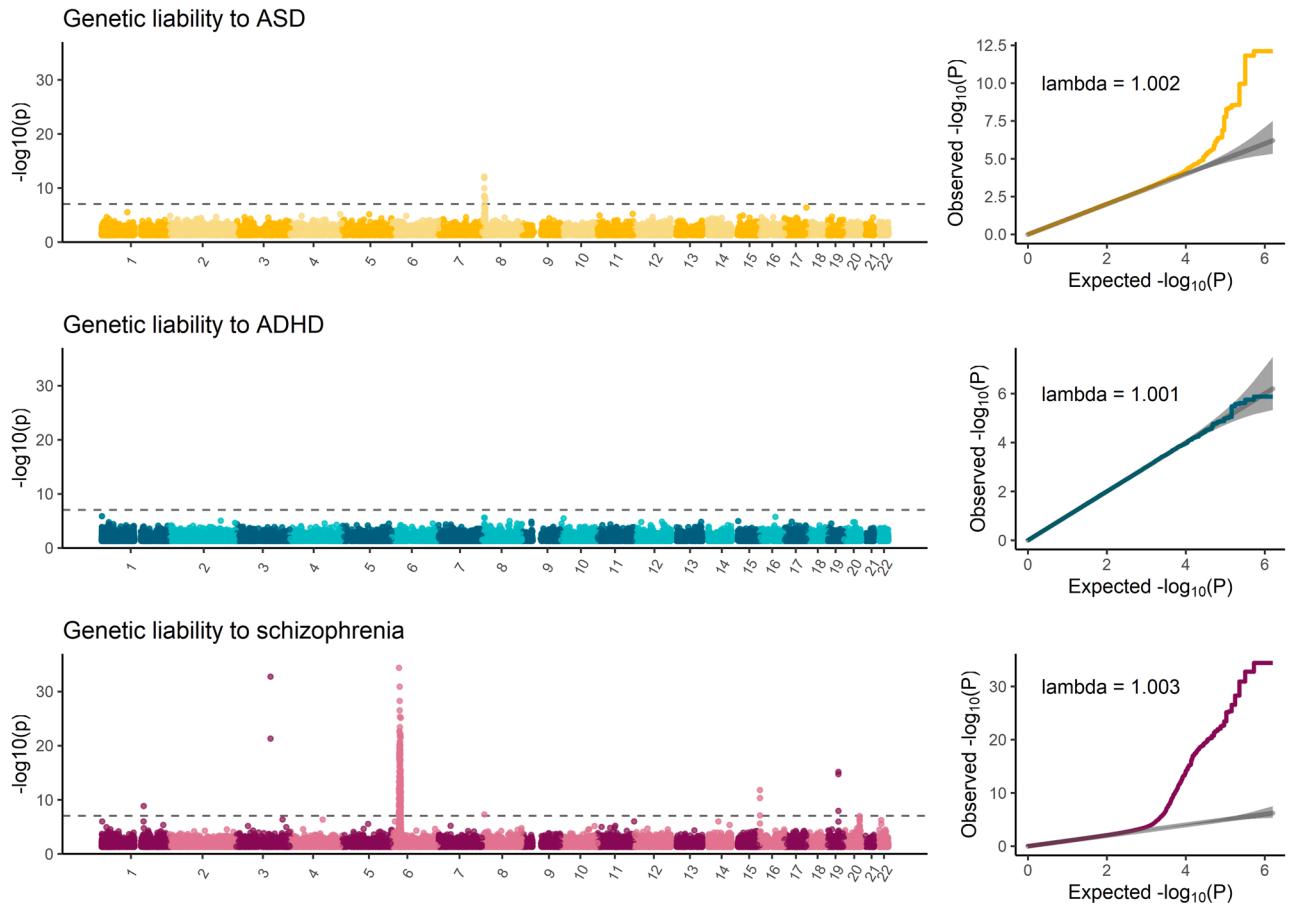

Figure 2. Manhattan plots and related quantile-quantile plots. Manhattan plots show which CpGs are associated with genetic susceptibility to neurodevelopmental conditions, with the gray dotted line indicating the epigenome-wide significance of $p < 9 \times 10^{-8}$. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

rs115329265 (6:28,712,247; more stringent) (18). We reran the EWAS in $GenR_{EPIC}$ using the original PGS SCZ, the PGS SCZ_{Rank1}, and the PGS $SCZ_{Variant}$. For the original PGS SCZ, we identified 9 EWAS-level hits ($p < 9 \times 10^{-8}$; 165 suggestive at $p < 5 \times 10^{-5}$). Of those, 4 were located in the MHC ($p < 9 \times 10^{-8}$; 53 suggestive). For the PGS SCZ_{Rank1}, we found 11 EWAS-level hits ($p < 9 \times 10^{-8}$; 171 suggestive), none of which resided within the MHC. Similarly, for the PGS $SCZ_{Variant}$, we identified 11 EWAS-level hits (all overlapping with PGS-SCZ_{Rank1}; $p < 9 \times 10^{-8}$; 172 suggestive), including one within the MHC. While EWAS-level hits were identical across both scores, 3 CpGs were uniquely identified at the suggestive threshold (Figure S2).

In region-level analyses (combining proximal CpGs into a smaller set of DNAm regions), a large number of DMRs were identified for all 3 PGSs, with 130 regions associated with the ASD PGS ($p < 9 \times 10^{-8}$; 251 at $p < 5 \times 10^{-5}$), 166 regions with the ADHD PGS (305 suggestive), and 157 regions with the SCZ PGS (297 suggestive, Tables S4–S6). Regions overlapped only slightly with probe-level results (genes overlapping between probe-level and region-level results: ASD PGS, 5.4%; ADHD PGS, 7.4%; SCZ PGS, 12.4%).

Follow-up analyses (Table 2) indicated that probes across all 3 PGSs showed greater genetic influence as expected (blood mQTLs, higher twin heritability estimates) and associations with gene expression compared with background signal. In addition, probe-level SCZ PGS sites, compared with ASD PGS and ADHD PGS sites, showed greater 1) blood-brain concordance, 2) representation of CoRSIVs, 3) enrichment for biological pathways (particularly related to adaptive immune response), 4) nonlinear change across childhood, and 5) more reported links to psychiatric disorders, neurocognitive conditions, and adversities, based on existing EWAS studies (Tables S1–S3). These patterns were largely driven by the MHC locus because the results were attenuated when analyses were restricted to suggestive SCZ PGS hits outside this locus ($GenR_{EPIC}$ only, Table S7).

Cross-NDC Comparisons

The ASD PGS and ADHD PGS ($r = 0.18$) were more strongly correlated with each other than with the SCZ PGS ($r = 0.08$–0.09, $p < .001$) (Figure 3A). Furthermore, while probe-level methylation patterns of genetic susceptibility for NDCs were largely unrelated, 3 suggestive sites ($p < 5 \times 10^{-5}$) were shared between the ASD PGS and the ADHD PGS (cg19034770, cg15741354, and cg11548083) but not

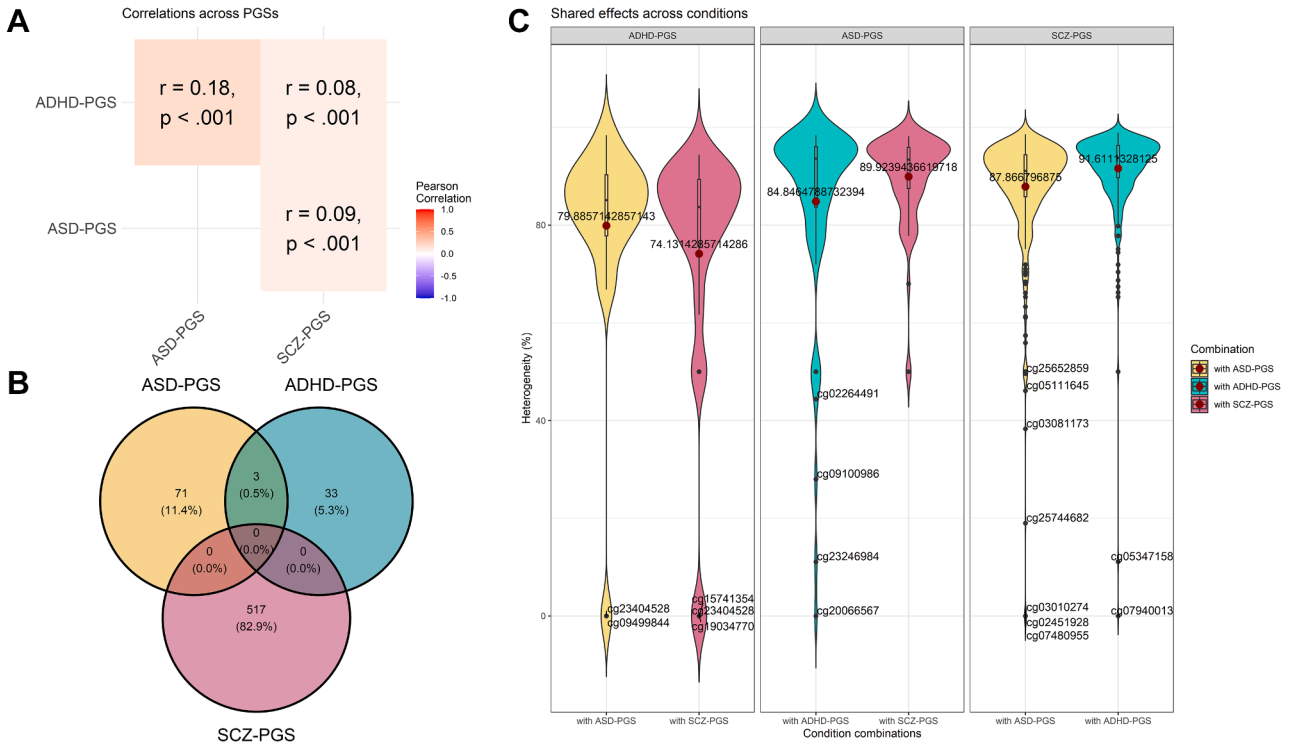

Figure 3. Cross-NDC comparisons for suggestive sites. **(A)** Correlations across genetic susceptibility (polygenic scores) for NDCs (meta-analyzed in a fixed effects model). **(B)** Suggestive CpGs that are shared across conditions ($p < 5 \times 10^{-5}$). **(C)** Heterogeneity (I^2) for suggestive sites. I^2 indicates the percentage of variability in associations between genetic susceptibility and DNA methylation of a given CpG across 2 conditions, which can be attributed to variability between genetic susceptibility to the 2 conditions. Therefore, a lower I^2 value reflects more similar effect sizes for a given CpG across the compared conditions. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; NDC, neurodevelopmental condition; PGS, polygenic score; SCZ, schizophrenia.

with the SCZ PGS (Figure 3B). A considerable proportion of variance in methylation patterns across PGSs could be attributed to heterogeneity (mean variability explained by heterogeneity > 74.1%) (Figure 3C and Table S8). Notably, only 7.5% of ASD PGS sites, 20% of ADHD PGS sites, and 4.8% of SCZ PGS sites were homogeneous across conditions (i.e., nonsignificant heterogeneity [$p > .05$] and consistent directional effects).

Phenotypic Associations

In our target sample ($GenR_{EPIC}$, $n = 1097$), MPSs were significantly correlated with their corresponding PGSs (PGS ASD: $r = 0.17$, $p < .001$; PGS ADHD: $r = 0.14$, $p < .001$; PGS SCZ: $r = 0.23$, $p < .001$). Combined, PGSs and MPSs accounted for up to 2.7% of variance in phenotypes beyond covariates, with MPSs uniquely contributing approximately 1 percentage point. The ASD PGS showed Bonferroni-corrected associations above covariates with 4 of 130 outcomes ($p < 8 \times 10^{-4}$; nominally at $p < .05$ with 20 of 130), the ADHD PGS with 11 of 130 outcomes (nominally 43 of 130), and the SCZ PGS with 1 of 130 outcomes (nominally 38 of 130), all above covariates. The MPSs did not show any Bonferroni-corrected associations above covariates and PGSs. Nominal increased variance ($p < .05$) was found for 1) the $MPS_{ASD\text{-}PGS}$ in ADHD symptoms, IQ, and number sequencing abilities; 2) the $MPS_{ADHD\text{-}PGS}$ in attention and total emotional and behavioral problems, ADHD diagnosis, language comprehension, number sequencing, height, and IQ; and 3) the $MPS_{SCZ\text{-}PGS}$ in child gross motor skills (Figure 4). Detailed results are shown in Tables S9–S11 and Figure S3.

DISCUSSION

We examined whether genetic susceptibility to NDCs is associated with DNAm patterns in cord blood, pooling data from 4 population-based cohorts totaling almost 6000 participants. Our meta-analytic EWAS revealed strong probe-level associations between genetic susceptibility to SCZ and neonatal DNAm (246 hits) compared with ASD (8 hits) and ADHD (none). SCZ PGS hits were mainly located within the MHC on chromosome 6, a well-established genetic risk locus for SCZ. In contrast to probe-level hits, region-level analyses detected many DMRs across all 3 PGSs (130–166 regions). PGSs showed little overlap in their DNAm associations, suggesting largely distinct epigenetic signals. Finally, DNAm-based scores of genetic susceptibility per NDC nominally increased variance in several developmental outcomes over the use of genetic data alone.

Our findings suggest that part of the polygenic contribution for SCZ is detectable epigenetically in the general population, even with a modest sample size relative to the case-control GWAS used to calculate the SCZ PGS ($n > 200{,}000$). Observing a strong signal already at birth provides additional

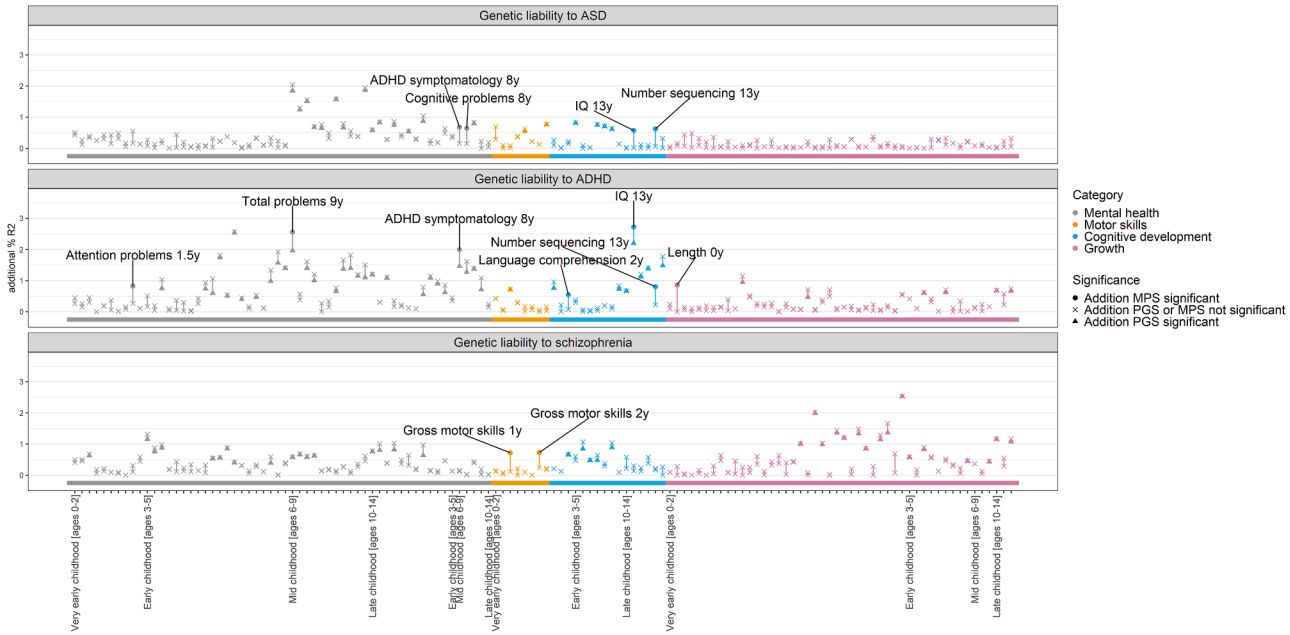

Figure 4. Phenotypic associations with genetic susceptibility (PGSs) to neurodevelopmental conditions and their MPSs in the target sample ($GenR_{EPIC}$) (n = 1097). Instances where the MPS explained additional phenotypic variance in addition to the PGS ($p < .05$) are indicated. More detail can be found in Tables S9 to S11. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; MPS, methylation profile score; PGS, polygenic score.

support for an early-origins perspective of SCZ (3). Previous studies have demonstrated that SCZ-associated genes are highly expressed in the placenta (28) and fetal brain (18,29); we extend these findings by showing that associations are also present at a gene regulatory level at birth. Perhaps unsurprisingly, our EWAS findings aligned closely with the discovery GWAS (18). Most identified hits clustered on chromosome 6, with 62% situated within the MHC (including our top hit cg14345882, $p = 3.9 \times 10^{-35}$, annotated to the promoter region of *BTN3A2*), likely because of the linkage disequilibrium pattern of this region. The MHC region is the strongest known genetic risk locus for SCZ (30), playing a key role in immune function [e.g., encoding proteins for antigen presentation (31)] alongside neurodevelopmental and brain-related processes [e.g., synaptic pruning (30)]. Other hits mapped to loci were linked to immune and neurodevelopmental functions, although not all GWAS peaks were mirrored epigenetically. Future work may clarify whether such discrepancies reflect timing, tissue specificity, or indirect pathways.

Substantially fewer hits were identified in the same sample for the ASD PGS and the ADHD PGS. These differences are unlikely to stem from a single definitive cause, but they may reflect a combination of methodological and biological factors. First, fewer hits might have been identified due to limited informativeness of the PGSs because of the smaller sample size of the discovery GWAS [ASD: 18,381 individuals diagnosed and 27,969 control participants; ADHD: 38,691 individuals diagnosed and 186,843 control participants; SCZ: 76,755 individuals diagnosed and 243,649 control participants (18–20)]. However, GWAS power does not entirely explain our pattern of findings because we identified no hits for the ADHD PGS but 8 hits for the ASD PGS (lowest GWAS sample size). All ASD PGS hits were located on chromosome 8 (1.0–1.9 Mb from ASD GWAS loci *C8orf74*, *SOX7*, *PINX1*) in *MFHAS1*, involved in modulating the innate immune system (32), and in/close to *FDFT1*, a gene implicated in the biosynthesis of cholesterol (33). The latter is noteworthy because of a potential role for cholesterol metabolism in ASD. For example, several ASD-related genetic syndromes such as fragile X syndrome and Smith-Lemli-Opitz syndrome involve disrupted cholesterol biosynthesis (34,35). Second, differences in hits across conditions may be due to the use of a different thresholding approach for the SCZ PGS (literature derived due to the lack of available phenotype data) compared with the ASD and ADHD PGSs (based on in-sample parameter optimization). Third, the biological relevance of DNAm in cord blood may differ across conditions. For example, many SCZ genetic susceptibility–associated CpGs mapped to immune-related pathways in the MHC region, a signal only seen for the SCZ PGS. Unlike the stark differences in signal observed at a probe level, we identified a similarly large number of DMRs across all 3 PGSs. Notably, probe-level and region-level results showed limited overlap, with each highlighting distinct sets of CpGs. Thus, our analyses identified both isolated CpGs with strong effects—particularly for SCZ—and more widespread, but weaker, epigenetic differences across conditions. These findings further indicate that the ASD PGS and ADHD PGS also associated with neonatal DNAm but that the epigenetic signal is more diffuse. It will be important for future research to understand to what extent differences in probe-level and region-level results are explained by methodological (e.g., power of PGS) versus biological (e.g., diffuse signals) reasons.

Three suggestive sites were linked to genetic susceptibility to both ASD and ADHD (cg11548083, cg19034770, and

cg15741354). Notably, cg11548083 is located on the *MSRA* gene, encoding methionine sulfoxide reductase A, an enzyme crucial for maintaining protein function and cellular integrity under oxidative stress, which has been implicated in biological aging (36). Interestingly, a previous cross-disorder GWAS reported that a SNP within *MSRA* was associated with both ASD and SCZ, but with opposing effects (37). Here, we observed similar opposing effects for this CpG, where the PGS ASD was associated with reduced DNAm levels, while notably, the PGS ADHD rather than the SCZ PGS was associated with increased DNAm levels. Beyond these shared sites, probe-level epigenetic signals exhibited only a little overlap across NDC PGSs. This may seem surprising given the known genetic (and phenotypic) correlations between ASD, ADHD, and SCZ. However, the magnitude of genetic correlations tends to be modest, as was also observed in our data, leaving far more variance that is unique to each condition.

We found that incorporating a DNAm-based measure of genetic susceptibility at birth in addition to PGSs could increase explained variance in developmental outcomes (nominal significance). While this finding is preliminary and in need of replication, it supports continued examination of the utility of integrating information on genetic susceptibility at multiple biological levels (PGS, DNAm) to enhance the performance of early risk prediction models. Although DNAm-based prediction tools are still emerging, they hold considerable promise, particularly if their development parallels the advances seen with PGSs (38). Future studies with more well-powered datasets may want to focus particularly on child attentional, cognitive, and motor outcomes rather than emotional/behavioral symptoms or general growth parameters because these showed the largest increases in explained variance compared with other phenotypes. Potentially, such phenotypes are more detectable due to biological differences (i.e., a more pronounced fetal neurodevelopmental component) or measurement-related factors, for example lower measurement error and reporting bias. In addition, DNAm-based measures of genetic susceptibility to ASD and ADHD both associated prospectively with ADHD-related phenotypes, whereas the DNAm-based measures of genetic susceptibility to SCZ only explained additional variance in early gross motor abilities. This is consistent with previous evidence showing that PGS SCZ correlated weakly with psychiatric symptoms in childhood (39) but associated with early motor abilities (40). The PGS SCZ and its corresponding MPS may become more predictive of mental health outcomes later in life because previous studies have linked genetic susceptibility to SCZ to a range of related outcomes, including depression and anxiety (41,42). Because our phenotypic data end at age 14, longer follow-up will be important to evaluate the predictive utility of SCZ PGS–associated methylation into adulthood. Importantly, only 1% to 10% of children will develop one of these NDCs (43), which raises questions about what factors interact with genetic susceptibilities to shape phenotypic expression during development and whether DNAm may be used in this context to improve risk stratification because it responds dynamically to both genetic and environmental influences.

Our findings need to be interpreted in light of some limitations. First, although we focused on genetic influences on DNAm (as captured by PGSs), this does not rule out potential perinatal environmental effects. In particular, it will be important to establish whether findings reflect direct or indirect effects of genetic susceptibility on DNAm. Additionally, we did not explicitly investigate genetic pleiotropy, and observed associations may be driven by related NDCs that were not measured (e.g., intellectual disability). Second, functional characterization of suggestive probe- and region-level sites was based on references largely derived from adult datasets, which may have more limited applicability to our neonatal datasets. Third, while we consider SCZ as an NDC, it is not included in this category in the DSM-5, and its conceptualization as neurodevelopmental remains a topic of debate. Fourth, our meta-analysis lacked non-European datasets, limiting extrapolation to other populations, and might have been influenced by selection bias, for example the overrepresentation of healthy newborns. Finally, while we identified numerous DNAm loci associated with genetic susceptibility to NDCs, based on the findings, we cannot ascertain their functional relevance or establish their role as a potential causal pathway to NDC pathophysiology as opposed to noncausal biomarkers for genetic susceptibility. Our work also opens several promising research avenues: 1) replication of findings and MPS effectiveness in other cohorts, particularly in case-control settings, biobanks, or with linkage to electronic health data, to confirm robustness of findings or when using more detailed epigenotyping, specifically whole-genome bisulfite sequencing, interrogating up to ~28 million CpGs, to provide a more comprehensive picture; 2) experimental validation of the identified DNAm sites or follow-up with transcriptome-wide association studies would be instrumental in clarifying their functional relevance; and 3) longitudinal follow-up of cohorts to assess the stability of these DNAm patterns over time and their impact on the phenotypic presentation of neurodevelopmental phenotypes would offer valuable insights into their developmental and mechanistic relevance.

Conclusions

By combining genetic and epigenetic data at birth, our findings lend novel insights into the early molecular correlates of genetic susceptibility to ASD, ADHD, and SCZ. We identified strong associations between the SCZ PGS and neonatal DNAm patterns in the general population, particularly within the MHC region, further supporting an early-origins perspective of SCZ and its links to adaptive immunity. Associations of neonatal DNAm with PGSs for ASD and ADHD were present but more diffuse, possibly reflecting differences in the power of the discovery GWAS. Epigenetic signals at birth were largely distinct between NDC PGSs. Finally, we found preliminary evidence that inclusion of methylation data may enhance genetic prediction models of neurodevelopmental outcomes.

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