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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Quality control for genotyping was performed using PLINK (version 1.07; http://pngu.mgh.harvard.edu/purcell/plink/, PMID: 17701901). Pre-phasing was done before imputation using SHAPEIT, and imputation was done using IMPUTE2 with Phase I 1000 genome as reference panel (PMID: 22384356, 22138821).
Data analysis	All statistical analyses were performed in the 'R' environment. We used the following 'R' packages: 'psych' Version = 1.5.8 (to calculate biserial correlation coefficients), 'limma' (PMID: 25605792), 'GenomicRanges' (PMID: 23950696), 'stats', 'BioMart' (PMID: 19617889, to identify genes mapping to specific loci). We performed pathway and functional analyses using the QIAGEN's Ingenuity® Pathway software (www.qiagen.com/ingenuity) and the Panther tool (release 20160321) on the Gene Ontology (GO) database (http://geneontology.org).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

In order to protect the privacy of the study participants, the genetic and ELCs data generated and analyzed during the current study are available from the corresponding author on reasonable request, together with the codes used for the analyses. The placental datasets and the other gene expression datasets analyzed in this study are available on the Gene Expression Omnibus repository (https://www.ncbi.nlm.nih.gov/geo/) under the accession codes provided in the manuscript.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size in the discovery sample was determined based on all the individuals with available good quality obstetrical histories data and genetic data, that were participants in the Clinical Brain Disorders Branch (CBDB) Sibling Study of Schizophrenia at the National Institute of Mental Health (NIMH; Clinical Brain Disorders Branch, protocol 95-M-0150, NCT00001486, Annual Report number: ZIA MH002942-03 CTNB). We performed replication analyses in 4 more independent samples, to support the reliability of our findings. Sample sizes in the replication samples were determined based on all the individuals with available good quality obstetrical histories data (i.e. assessable with the McNeil-Sjostrom scale) and genetic data in the Psychiatric Genetic Consortium, and in our collaboration network. To further support the reliability of our findings, we also performed the analyses in the merged sample.
Data exclusions	We excluded from our analysis individuals for which it was not possible to establish the presence or absence of at least one serious early life complication (ELC), based on the available data. For genotyping quality control, we excluded individuals with missing rate higher than 2% and extreme heterozygosity values (±3 SD). For calculation of polygenic risk scores, we excluded SNPs if they failed Hardy-Weinberg equilibrium test (P < 10−6 in controls or P < 10−10 in cases) and if they had minor allele frequency less than 1%. Quality control for genotyping was performed consistent with previous reference (PMID: 25056061). Since only SNPs mapping to autosomal chromosomes are used for schizophrenia PRS construction, we excluded - from the selection of genes mapping to PRS loci - the genes that were irrelevant to our question, i.e. genes mapping to mitochondrial DNA, and X and Y-chromosome genes or other genes mapping to loci not used for PRS's calculation, thus avoiding the risk of overinflating p-values (https://bioconductor.org/packages/release/bioc/vignettes/GOstats/inst/doc/GOstatsHyperG.pdf). All the study participants were unrelated.
Replication	The interaction between polygenic score for schizophrenia (PRS) and ELCs found in the discovery sample was reliably replicated in two more independent samples.The relationship between PRS and ELCs in patients with schizophrenia, detected in the discovery sample, was reliably replicated in four independent samples.
Randomization	In each analysis, we used 10 ancestry-based principal components as covariates, to avoid potential confounding effects of population stratification, consistent with previous work (PMID: 25056061). We performed sensitivity analyses adding sex and age, maternal and paternal ages, maternal stress, substance use history and socioeconomic status, as covariates, and also their interaction with PRS and ELCs, as recommended to properly exclude the role of confounders (PMID: 24135711).
Blinding	The investigators who performed the recruitment and the clinical evaluation of controls and patients with schizophrenia were blinded to their PRS's and ELCs. PRS's were unknown to both the individuals who provided the information about ELCs and to the researchers who collected and evaluated them. ELCs histories were unknown to the investigators that calculate PRS's.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☒	☐ Unique materials
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Research animals
☐	☒ Human research participants

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	No cell lines were used. We just analyzed cell line data publicly available.
Authentication	No cell lines were used. We just analyzed cell line data publicly available.
Mycoplasma contamination	No cell lines were used. We just analyzed cell line data publicly available.
Commonly misidentified lines (See ICLAC register)	No cell lines were used. We just analyzed cell line data publicly available.

Human research participants

Policy information about studies involving human research participants

Population characteristics	All relevant information on human research participants are provided in the On-line methods section and in Table S2.

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ Magnetic resonance imaging