nature portfolio

Corresponding author(s): Nikos Stratakis

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Reporting Summary

Nature Portfolio 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 Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the 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
☐	☒	A statement on 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 statistical parameters 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

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	N/A
Data analysis	The software program and packages used to conduct the present analyses are freely available and can be found via the citations in the manuscript. The code used for the present analysis can be found at: Stratakis N. Multi-omics architecture of obesity and metabolic dysfunction: identifying biological pathways and prenatal determinants. nstrata/multiomics_childhood_obesity. https://doi.org/10.5281/zenodo.14354199.

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Due to the HELIX data policy and data use agreement, human subjects' data used in this project cannot be freely shared. Researchers external to the HELIX Consortium who have an interest in using data from this project for reproducibility or in using data held in general in the HELIX data warehouse for research

purposes can apply for access to data for a specific manuscript at the time. Interested researchers should fill in the application found at https://www.projecthelix.eu/files/helix_external_data_request_procedures_final.pdf. and send it to helixdata@isglobal.org. The applications are received by the HELIX Coordinator, and are processed and approved by the HELIX Project Executive Committee. The decision to accept or reject a proposal is taken by the HELIX Project Executive Committee, and is based largely on potential overlap with other HELIX-related work, the adequacy of data protection plans, and the adequacy of authorship and acknowledgement plans. Further details on the content of the data warehouse (data catalogue) including those data used for the present study and procedures for external access are described on the project website https://www.projecthelix.eu/es/data-inventory. Source data are provided as a Source Data file.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	In this study, we used the term sex to denote a biological attribute of the participants. Our study populations were drawn from population-based cohorts where sex was neither an inclusion nor exclusion criterion during recruitment and follow-up data collection. The sex of each participant was recorded during clinical examinations conducted as part of each cohort study. We accounted for potential confounding by sex in all primary analyses.
Reporting on race, ethnicity, or other socially relevant groupings	In the present study, we presented race/ethnicity as white people, South Asian, or other. This information was provided by participants during the clinical examination of each participating cohort. We accounted for potential confounding by race/ethnicity in all primary analyses.
Population characteristics	This study used data collected in the HELIX project,a collaboration across six established and ongoing longitudinal population based cohorts, involving children from two large parts of Europe: the Northern/Western (N/W) part (study sites: Born in Bradford (BiB) cohort study, Bradford, UK; Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant (EDEN) cohort study, Poitiers, France; Kaunas cohort (KANC) study, Kaunas city, Lithuania; and Norwegian Mother, Father and Child (MoBa) cohort study, Oslo, Norway83) and the Southern/Mediterranean (S/M) part (study sites: INfancia y Medio Ambiente (INMA) cohort study, Sabadell, Spain; and RHEA Mother Child cohort study, Heraklion, Greece). These cohorts were selected for participation in the HELIX project because: (a) they could provide substantial existing longitudinal data from early pregnancy through childhood, (b) they could follow-up children at similar ages, (c) they could integrate questionnaires, biosampling and clinical examinations using common HELIX protocols and (d) they offered heterogeneity in terms of exposure and population characteristics.From the entire cohort, a subcohort of mother-child pairs was selected to be fully characterised for a broad suite of environmental exposures and 'omics' data, to be clinically examined and to have biological samples collected.
Recruitment	A new follow-up visit was organised for these mother-child pairs between December 2013 and February 2016. Subcohort subjects were recruited from within the entire cohorts such that there were approximately 200 mother-child pairs from each of the six cohorts. Subcohort recruitment in the EDEN cohort was restricted to the Poitiers area and in the INMA cohort to the city of Sabadell.
Ethics oversight	Local ethical committees approved the studies that were conducted according to the guidelines laid down in the Declaration of Helsinki. The ethical committees for each cohort were the following: BIB: Bradford Teaching Hospitals NHS Foundation Trust, EDEN: Agence nationale de sécurité du médicament et des produits de santé, INMA: Comité Ético de Inverticación Clínica Parc de Salut MAR, KANC: Kaunas Regional Committee for Biomedical Research Ethics, MoBa: Regional komité for medisinsk og helsefaglig forskningsetikk, Rhea: Ethical committee of the general university hospital of Heraklion, Crete.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

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

Sample size	The present study includes 863 participants with available information on five molecular layers (dna methylation, mirnas, gene expression, proteins, metabolites), on clinical and metabolic phenotyping, and on prenatal environmental exposures.
Data exclusions	Eligibility criteria for inclusion in the HELIX subcohort were: (a) age 6–11 years at the time of the visit, with a preference for ages 7–9 years if possible; (b) sufficient stored pregnancy blood and urine samples available for analysis of prenatal exposure biomarkers; (c) complete address history available from first to last follow-up point; (d) no serious health problems that may affect the performance of the clinical testing or impact the volunteer's safety (eg, acute respiratory infection). In addition, the selection considered whether data on important covariates (diet, socioeconomic factors) were available. Each cohort selected participants at random from the eligible pool in the entire cohort and invited them to participate in this subcohort until the required number of participants was reached. For the present study, we excluded participants with no available information for the variables of interest (omics, adiposity and metabolic health outcomes, prenatal environmental factors).
Replication	During the follow-up examination of each participating cohort, trained nurses interviewed the mothers, carried out health examinations of the

children and collected biological samples using harmonised and standardised operating procedures.

Randomization: N/A

Blinding: N/A

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks: *Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*

Novel plant genotypes: *Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*

Authentication: *Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*