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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	R (4.2.1)
Data analysis	R (4.2.1), MATLAB R2021b, SPM12

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

The main statistical data that support the findings of this study are available (Supplementary Tables 1-24). The DNA methylation microarray data supporting the findings of this study have been deposited in the Gene Expression Omnibus (GEO) database under the Super Series accession number GSE239522 (SubSeries: GSE239517, GSE239518, GSE239520, and GSE239521). For additional information regarding access to these data, please contact the corresponding authors.

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	This study did not analyze by sex. However, we did include the sex as a covariate in the genome-wide analysis. This information on sex we collected based on self-report. However, the data from methylation EPIC array allowed us to confirm the sex chromosomes, and there were no sex mismatches.
Reporting on race, ethnicity, or other socially relevant groupings	All subjects in this study were Japanese descendant.
Population characteristics	Group (child maltreatment and typically developing), Age, sex, IQ (intellectual quotient), and DQ (developmental quotient).
Recruitment	Judicial Autopsy Cases Twenty-six children authenticated by a forensic pathologist (M.N.) during 2000-2021 were included. Of these, 15 (CM) cases had cause of death due to child abuse and the other 11 (TD) cases were due to fatal accidents or illness (Supplementary Table 23). Toddler Social Cognition and Adolescent Brain Imaging cohorts Children sheltered in residential childcare facilities were recruited as case (CM), and children raised in biological families from the local community were recruited as control (TD).
Ethics oversight	Judicial Autopsy Cases The protocol for this study was approved by the Ethics Committee of the University of Fukui (approval no. 20200030) and the Research Ethics Review Board of Hiroshima University (approval no. E-2032) and was conducted in accordance with the Declaration of Helsinki. Toddler Social Cognition cohort The protocol of this cohort study was approved by the Ethics Committee of the University of Fukui (approval nos. 20140142, 20150068, and 20190107) and was conducted in accordance with the Declaration of Helsinki. All parents or child-care facility directors provided written informed consent to participate in the study. Adolescent Brain Imaging cohort The protocol of this cohort study was approved by the Ethics Committee of the University of Fukui (approval nos. 20110104, 20130157, 20138031, 20150068, 20190107, 20210004, 20220034, and 20220039) and conducted in accordance with the Declaration of Helsinki. All parents or child-care facility directors provided written informed consent to participate in the study.

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	Judicial Autopsy Cases No sample size calculation was performed since this was highly limited to the accumulation of rare judicial autopsy cases over about 20 years. Toddler Social Cognition and Adolescent Brain Imaging cohorts No sample size calculation was performed. However, it was extremely difficult to collect a sample from maltreated children who received interventions (in fact, this sample size took about 10 years), and the sample size was not inferior to the sample sizes of other similar prospective studies subjected to children (not retrospective adult) listed below. This study is also the largest study in which methylation arrays of abused children are performed simultaneously with brain MRI and other intermediate phenotype data acquisition. Yang BZ, et al. Child abuse and epigenetic mechanisms of disease risk. Am J Prev Med 44, 101-107 (2013). Kumsta R, et al. Severe psychosocial deprivation in early childhood is associated with increased DNA methylation across a region spanning the transcription start site of CYP2E1. Transl Psychiatry 6, e830 (2016). Papale LA, Seltzer LJ, Madrid A, Pollak SD, Alisch RS. Differentially Methylated Genes in Saliva are linked to Childhood Stress. Sci Rep 8, 10785 (2018). Naumova OY, et al. Effects of early social deprivation on epigenetic statuses and adaptive behavior of young children: A study based on a cohort of institutionalized infants and toddlers. PLoS One 14, e0214285 (2019). Cicchetti D, Hetzel S, Rogosch FA, Handley ED, Toth SL. An investigation of child maltreatment and epigenetic mechanisms of mental and

physical health risk. Dev Psychopathol 28, 1305-1317 (2016).
Sumner JA, Gambazza S, Gao X, Baccarelli AA, Uddin M, McLaughlin KA. Epigenetics of early-life adversity in youth: cross-sectional and longitudinal associations. Clin Epigenetics 14, 48 (2022).

Meta-analysis
No sample size calculation was performed. The previous study below is a longitudinal meta-analysis as secondary analysis of three previously published data, while this study is a cross-sectional meta-analysis of three original data, and thus differs in this regard, but with a sample size not that different from that of the present meta-analysis. As all of the data in this study are our own primary data, the preprocessing was conducted using the identical process, which is also consistent with the strategy taken by this previous study.

Data exclusions

Judicial Autopsy Cases
No data were excluded from the analysis.

Toddler Social Cognition cohort
One hundred and twenty-two children aged 0–9 years participated in this cohort during 2017-2021 with an assessment of social cognitive function by gaze patterns and buccal mucosa sampling. The methylation analysis in this study was conducted on 85 participants (CM:36, TD:49) who met the criteria of maltreatment experiences, passed the data QC as described "Quality control (QC) procedures for blood, buccal, and saliva", including a not repeated measurement, and were assessed using a full-scale intelligent quotient (FSIQ) or developmental intelligence quotient (DQ) with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV), Kyoto Scale of Psychological Development (KSPD), or other scales (Table 1).

Adolescent Brain Imaging cohort
Brain imaging (No data were excluded from the analysis)
Two hundred and thirty-seven children and adolescents aged 6–18 years (CM:83, TD:154) participated in this cohort during 2013-2022 by undergoing a brain MRI (Supplementary Table 24). Group comparisons of the brain GM structures were conducted using the full set of data.

Methylation
Saliva was collected from 141 of these participants and the methylation analysis in this study was conducted on 123 participants (CM:61, TD:62) within this subset who met the criteria of maltreatment experiences, passed the data QC as described "Quality control (QC) procedures for blood, buccal, and saliva", including not repeated measurements, and FSIQ assessment (Table 1).

Imaging epigenetics
A total of 119 individuals (CM:58, TD:61) underwent both brain MRI and saliva collection and were available for imaging epigenetics analysis.

Replication

This study conducted two reproducibility tests on the results of the meta-analysis. The first was to evaluate the reproducibility of the four CpGs most significant in the meta-analysis on publicly available data sets (GSE118940). Second, the CpGs reported in five independent studies were evaluated using the framework of our meta-analysis (Supplementary Table 22).

Randomization

This study is consisted by multi cross-sectional case-control studies. Thus, randomization was not necessary.

Blinding

The investigators were not blinded to group allocation during data collection and analysis. This study has been conducted in clearly separated case and control groups during data collection, and because it has been shared among the team.

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

Magnetic resonance imaging

Experimental design

Design type

T1-weighted structural imaging

Design specifications

Not applicable (did not conduct tasks)

Behavioral performance measures

Not applicable (did not conduct tasks)

Acquisition

Imaging type(s)	T1-weighted structural imaging
Field strength	3T
Sequence & imaging parameters	GE Discovery MR750 pulse sequence type: fast-spoiled gradient recalled imaging sequence imaging type: T1W gradient echo images field of view: 256 mm matrix size: 256 × 256 matrix slice thickness: 1 mm orientation and TE/TR/flip angle: orientation, TE = 1.99 ms, TR = 6.38 ms, flip angle = 11◦ GE Signa PET/MR pulse sequence type: fast-spoiled gradient recalled imaging sequence imaging type: T1W gradient echo images field of view: 256 mm matrix size: 256 × 256 matrix slice thickness: 1 mm orientation and TE/TR/flip angle: orientation, TE = 3.24 ms, TR = 8.46 ms, flip angle = 11◦
Area of acquisition	Whole brain scan was used.

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	Voxel-based morphometry (VBM) implemented in Statistical Parametric Mapping (SPM) 12 (Wellcome Trust Centre for Neuroimaging, London, UK) with MATLAB R2021b (MathWorks, Natick, MA, USA) was used. The images were segmented into gray matter (GM), white matter, cerebrospinal fluid, and skull/scalp compartments using tissue probability maps. The Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) algorithm was applied to the segmented brain tissues to generate a study-specific template and to achieve an accurate inter-subject registration with improved realignment of smaller inner structures. Spatially normalized GM images were smoothed using a Gaussian kernel with a full width at half maximum of 10 mm.
Normalization	The segmented GM images were spatially normalized with an isotropic voxel resolution of 1.5 mm.
Normalization template	ICBM152
Noise and artifact removal	Not applicable (did not conduct fMRI)
Volume censoring	Not applicable (did not conduct fMRI)

Statistical modeling & inference

Model type and settings	Regional differences in GM volume between cases and controls were analyzed in SPM12 using multiple regression analyses.
Effect(s) tested	Group (cases and controls) was modeled as the independent variable, GM volume as the dependent variable, and age, FSIQ, scanner type, and total GM volume as potential confounding effects.

Specify type of analysis: ☒ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016)	All of the voxels in the whole brain with a voxel-wise threshold of $P < 0.001$ and the voxels determining a cluster-wise corrected $P < 0.05$, using cluster size.
Correction	The statistical threshold for height was corrected to $P < 0.05$ for multiple comparisons using cluster size.

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis