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Cohort Profile

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Cohort Profile: The Environment and Development of Children (EDC) study: a prospective children's cohort

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Why was the cohort set up?

Exposure to environmental risk factors during the prenatal and early childhood period can lead to physical and neurobehavioural developmental abnormalities[1,2] among children, which can persist into adulthood.[3,4] This finding emphasizes the importance of early environmental chemical exposure and suggests an underlying mechanism for its persisting effects during vulnerable periods.[5,6] Epigenetic processes have been suggested to mediate the lasting effects of environmental chemical exposure on the developmental trajectories of children.[7] However, previous birth cohort studies have not thoroughly investigated the vulnerable periods of environmental exposure or the underlying mechanism for the lasting effects of environmental chemical exposure.[8–10]

The development of children should be comprehensively evaluated, especially in terms of physical and neurobehavioural aspects. In particular, among various neurobehavioural outcomes, autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) attract increasing attention as they are major public health problems worldwide, impose substantial social burden and are associated with environmental chemical exposure.[11–13] However, the aetiologies of these disorders are largely unknown, possibly because ASD and ADHD frequently co-occur and have been suggested to represent a continuum between normal and severe disability.[14,15] Additionally, previously conducted studies mostly used a case–control design, which resulted in the exclusion of children whose symptoms change over time.[16]

Therefore, we conducted the Environment and Development of Children (EDC) cohort study to investigate the associations between environmental risk factors and physical and neurobehavioural developments (including phenotypic features related to ASD and ADHD) of children, with a particular focus on the window of vulnerability[17] and the role of epigenetic changes as a mechanism underlying the

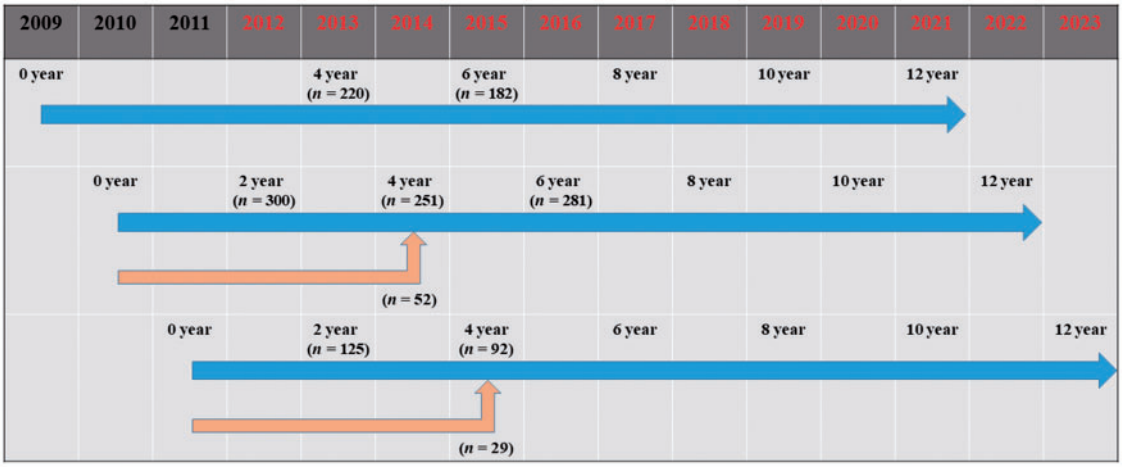

Figure 1. Diagram of the protocol and timeline of the Environment and Development of Children (EDC) study.

lasting effects of environmental exposure.[18] The overall purposes of the EDC study are to: (i) obtain information on the levels and sources of environmental risk factors during the prenatal–early childhood period; (ii) assess the association between environmental risk factors and physical and neurobehavioural developments of children; (iii) evaluate the susceptibility period for each environmental risk factor; and (iv) investigate the possibility of genome-wide DNA methylation profile as an underlying basis for the lasting effects of environmental chemical exposure on the developmental trajectories of children.

Who is in the cohort?

The EDC study was designed to enrol children from the 13 484 mother–child pairs who participated in the Congenital Anomaly Study (CAS). The CAS recruited pregnant women from eight local hospitals in the Seoul and Gyeonggi province of the Republic of Korea between August 2008 and July 2010, to investigate the association between prenatal environmental exposure and risk of congenital deformity at birth. In the CAS, maternal spot urine and peripheral blood samples were collected from pregnant mothers upon enrolment (during the second trimester of pregnancy, between 14 and 27 weeks of gestation, with a mean of 20 weeks), along with their sociodemographic and lifestyle factors and previous medical history data.

After the CAS ended in 2011, we started the EDC study to further evaluate the potential harmful effects of environmental risk factors on children. Children who had a congenital deformity at birth ($n = 115$) or invalid contact information ($n = 218$) were excluded. We individually explained the purpose of the EDC study to parents with 2–4-year-old children who were randomly selected from the CAS participants list through telephone calls. Subsequently, 645 children were enrolled after contacting 2085 mothers between 2012 and 2013. Compared with CAS-participating mothers with children not enrolled in the EDC study, mothers with children enrolled in the EDC study were more likely to drink alcohol regularly (26.0% vs 22.1%). However, the proportion of active smokers (6.1% vs 5.9%), proportion of caesarean section deliveries (35.2% vs 33.5%), maternal age at enrolment (31.4 years vs 30.5 years) and birthweight (3.2 kg vs 3.2 kg) did not differ appreciably between mothers with children enrolled and not enrolled in the EDC study. The sample size was originally estimated to evaluate the association between exposure to endocrine–disrupting chemicals (bisphenol A) and body mass index of the children. We obtained a sample size of 610, with an effect size of 0.017,[19] a power of 90% and a confidence interval of 95%. To allow a follow-up loss of 5%, a sample size of 645 children was determined.

A total of 425 children aged 2 years were enrolled. Of these children, 300 and 125 were enrolled in 2012 and 2013, respectively. Furthermore, 220 children aged 4 years were enrolled in 2013. To compensate for losses by the time of follow-up, we enrolled additional 52 and 29 children in 2014 and 2015, respectively, using the same eligibility criteria and processes. All children enrolled in 2014 and 2015 were 4 years of age. Therefore, in total, 726 children aged 2–4 years were recruited and comprised the final participants in the EDC study (Figure 1).

Table 1 presents the baseline characteristics of the EDC study participants. Of the 726 enrolled children, 377 (51.9%) were boys, 255 (35.2%) were born via caesarean section and 81 (11.8%) were not breastfed. The mean birthweight of the participants was 3.2 kg. During pregnancy, 23 mothers (3.2%) experienced gestational diabetes. The majority of fathers (83.6%) and mothers (81.3%) have at least a college education. Among the 425 children at 2 years of age, 223 (52.5%) were boys, and the mean

Table 1. Baseline characteristics of children and parents participating in the Environment and Development of Children (EDC) study

Characteristics	Total ($n = 726$)[a]
Children's sex	
Boy	377 (51.9)
Girl	349 (48.1)
Type of delivery	
Vaginal delivery	470 (64.8)
Caesarean delivery	255 (35.2)
Birthweight (kg)	3.2 (1.2)
Feeding method	
Breastfeeding	224 (32.7)
Combined feeding	380 (55.5)
Drieded milk	81 (11.8)
Duration of breastfeeding (months)	9.6 (6.7)
Maternal education level	
Less than high school	1 (0.1)
High school	135 (18.6)
College or more	590 (81.3)
Paternal education level	
Less than high school	2 (0.3)
High school	117 (16.1)
College or more	606 (83.6)
Gestational diabetes	
No	703 (96.8)
Yes	23 (3.2)

[a]Values are presented as *n* (%) or means (standard deviations).

(standard deviation) height, weight and bone age were 86.3 (3.2) cm, 12.3 (1.4) kg and 25.1 (4.4) months, respectively. Among the 644 children at 4 years of age, 337 (52.3%) were boy, and the mean height, weight and bone age were 102.0 (3.7) cm, 16.3 (1.9) kg and 48.1 (6.2) months. Based on the results of the physical examinations conducted by paediatric endocrinologists, 10 children (1.6%) exhibited abnormal testicular volume and one child (0.2%) had abnormal breast development. The mean (standard deviation) intelligence quotient (IQ) scores of the children at 6 years of age ($n = 176$) and their mothers ($n = 176$) were 109.0 (11.8) and 117.0 (12.4), respectively.

The EDC study protocol was reviewed and approved by the Ethics Review Board of Seoul National University Hospital (C-1201–010-392). All participating parents provided written informed consent at every survey.

How often have they been followed up?

We conducted follow-up surveys with 2-year intervals (Figure 1). Among the 425 children who were enrolled at 2 years of age, 343 were followed up at 4 years of age (follow-up rate: 80.7%). Currently, we plan to follow these children until they reach 12 years of age in 2023.

To maintain our follow-up rate, we particularly pay attention to keeping constant contact with participants using various modalities such as telephone, mails which report health examination results, newsletters and birthday cards. We contacted the participants via telephone approximately 1 month before the survey. If we were unable to contact the participants during the first attempt, we attempted to re-contact them up to three times at different times on different days. After we contacted the participants via telephone, we mailed a questionnaire to be filled out by the parents before every visit. Moreover, we verified the answers through face-to-face interviews which were conducted by trained interviewers. We also regularly sent health examination results, newsletters and birthday cards by mail.

What has been measured?

We obtained the information concerning obstetric history and birth outcomes, such as birthweight and height, from medical records. For each survey, a structured questionnaire was used to gather information on sociodemographic and lifestyle factors, previous personal and family medical histories and environmental exposures.

Blood and urine samples were also collected at every survey between 9:00 am and 12:00 pm after an overnight fast at Seoul National University Children's Hospital. The glucose and insulin levels; thyroid, liver, and renal functions; lipid profiles and adipokine levels; and inflammatory markers were analysed at Seoul National University Hospital. The residual samples were stored in a freezer at –20°C and transferred to external analysis laboratories (Eulji University, Seongnam, Republic of Korea; Green Cross Laboratories, Yongin, Republic of Korea; SPL Lifesciences, Pocheon, Republic of Korea; Seegene Medical Foundation, Seoul, Republic of Korea) for measurements of the levels of urinary bisphenol A, urinary phthalate metabolites, urinary 3-phenoxybenzoic acid, blood heavy metals and serum perfluorinated compounds (Table 2). These environmental chemicals were selected with consideration to their clinical and public health implications, that resulted from their widespread use in consumer products, and their reported adverse health outcomes even at low concentrations.

The dietary information of children aged ≥4 years was collected from their mothers using a semi-quantified food frequency questionnaire, which evaluated the food consumption frequency and portion sizes. Their food and nutritional intake was estimated using the Computer Aided Nutritional Analysis Program 4.0 for Professionals (Korean Society of Nutrition, Seoul, Republic of Korea).

The heights (cm) and weights (kg) of the participants were measured to one decimal place using a Harpenden Stadiometer (Holtain Ltd, Crymych, UK) and digital scale,

Table 2. Exposures and outcomes evaluated in the Environment and Development of Children (EDC) study

	Prenatal	2 years	4 years	6 years
Exposures				
Bisphenol A	√	√	√	√
Phthalates (MEHHP, MEOHP, MnBP)	√	√	√	√
Phthalates (MECPP, MBzP)			√	√
3-phenoxybenzoic acid	√	√	√	√
Heavy metals (Pb, Hg, Cd, Mn)	√		√	√
Heavy metals (As[a])			√	√
Perfluorinated compounds[b]		√	√	√
Dietary information			√	√
Outcomes				
Growth		√	√	√
Neurobehavioural tests				√
Biochemical tests		√	√	√
DNA methylation				√

MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MnBP, mono-n-butyl phthalate; MECPP, Mono-(3-carboxypropyl) phthalate; MBzP, mono-benzyl phthalate.

[a]The total arsenic, trivalent arsenic (As3+), pentavalent arsenic (As5+) and dimethyl arsenic (DMA) levels were measured.

[b]The perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), perfluorotetradecanoic acid (PFTeDA), L-perfluorobutanesulphonate (L-PFBS), L-perfluorohexanesulphonate (L-PFHxS), L-perfluorooctanesulphonate (L-PFOS), and perfluorodecane sulphonate (PFDS) levels were measured.

respectively. Their waist circumferences were obtained at the minimal waist. Additionally, the bone ages of the participants, which reflect skeletal maturation,[20] were also assessed. The body composition measurements were conducted via bioelectrical impedance analysis using an InBody 770 device (Biospace Co., Seoul, Republic of Korea). The blood pressure measurements of the children aged ≥4 years, which were performed twice in a resting state, were analysed. Children aged ≥8 years underwent pulmonary function tests (spirometry). The anthropometric indices, blood pressure and pulmonary functions were measured by trained medical personnel at Seoul National University Hospital. All participants underwent physical examinations, including thyroid palpation and puberty staging based on breast/genital development and pubic hair growth, which were conducted by a paediatric endocrinologist.

We evaluated the neurobehavioural development of children at 6 and 8 years of age. For children aged 6 years, we used the Social Communication Questionnaire to evaluate the ASD features, with a focus on social communication impairment. Following the screening of all children using the Social Communication Questionnaire, those who were at risk of ASD underwent further evaluation using the Autism Diagnostic Observation Schedule tool. The ADHD Rating Scale, Comprehensive Attentional Test Battery and Stroop Colour and Word Test were used to evaluate executive dysfunction and attentional impairment, which are known to be core deficits associated with ADHD. We also measured the IQ of the children using the Korean Educational Developmental Institute's Wechsler Intelligence Scale for Children. Furthermore, we also measured the IQ of the mothers using the Korean Wechsler Adult Intelligence Scale IV, to control the influence of maternal IQ on children's IQ. For children aged 8 years, we assessed the frontal lobe function using the Wisconsin Card Sorting Test. Subsequently, these children were evaluated for internet and smartphone addiction using the K- and S-scales, respectively. These tests were conducted by paediatric psychiatrists and clinical psychologists at Seoul National University Hospital.

Environmental pollutant exposure, especially during vulnerable period, can change epigenetic features such as DNA methylation,[21,22] which in turn may affect long-term trajectories of physical and neurobehavioural development.[7] Although there can be organ specificity in the epigenetic features, many cohort studies assessed DNA methylation profile using blood samples, for feasibility reasons.[21–24] In addition, previous studies have reported associations between DNA methylation changes in the peripheral blood and various health outcomes.[25–27] In the EDC study, the genomic DNA was extracted from the blood samples of 6-year-old children using the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA). Bisulphide conversion was conducted using the EZ DNA Methylation Kit (Zymo Research Co., Irvine, CA, USA). Genome-wide DNA methylation was analysed using the Infinium HumanMethylation450 BeadChip (Illumina Inc., San Diego, USA). Meanwhile, the performance of

Table 3. Selected environmental pollutant concentrations of the Environment and Development of Children (EDC) study participants in the prenatal period and at 2, 4, and 6 years of age

Age (year)	*n*	Mean	SD	Median	IQR
Bisphenol A (μg/g creatinine)					
Prenatal	658	2.4	3.3	1.3	1.9
2	321	12.5	32.8	6.4	7.4
4	644	6.2	17.6	3.7	4.0
6[a]	181	3.2	3.7	2.3	2.4
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (μg/g creatinine)					
Prenatal	638	22.4	42.8	16.6	16.8
2	324	111.2	89.5	91.6	78.4
4	644	96.0	194.2	68.7	53.2
6[a]	181	72.7	41.4	65.8	34.7
Mono-(2-ethyl-5-oxohexyl) phthalate (μg/g creatinine)					
Prenatal	638	21.7	33.5	16.2	15.2
2	324	92.4	82.8	72.9	59.7
4	644	71.4	110.6	54.3	41.6
6[a]	181	54.4	30.6	49.0	28.8
Mono-n-butyl phthalate (μg/g creatinine)					
Prenatal	638	61.4	104.1	40.0	32.5
2	324	128.4	71.5	117.1	80.0
4	644	102.6	78.2	84.5	68.4
6[a]	181	92.6	55.9	81.2	43.6
Mono-(3-carboxypropyl) phthalate (μg/g creatinine)					
4	120	122.2	76.6	97.2	62.0
6[a]	181	115.5	79.1	102.8	66.1
Mono-benzyl phthalate (μg/g creatinine)					
4	119	10.5	16.8	6.3	7.7
6[a]	175	12.5	29.8	5.3	8.5
3-phenoxybenzoic acid (μg/g creatinine)					
2	304	2.5	7.0	1.2	1.5
4	643	2.4	4.4	1.4	1.7
6[a]	181	1.8	3.1	1.0	1.1
Lead (μg/dl)					
Prenatal	635	1.4	0.4	1.3	0.5
4	118	1.5	0.5	1.4	0.5
6[a]	456	1.5	0.6	1.5	0.6
Mercury (μg/l)					
Prenatal	635	2.7	1.5	2.4	1.4
4	118	1.9	0.8	1.8	0.7
6[a]	456	1.8	0.9	1.6	0.9
Cadmium (μg/l)					
Prenatal	635	0.7	0.3	0.6	0.4
4	118	0.2	0.2	0.2	0.1
6[a]	456	0.2	0.1	0.2	0.1
Manganese (μg/dl)					
Prenatal	635	13.4	4.8	12.5	5.6
4	118	1.3	0.3	1.2	0.3
6[a]	456	1.3	0.3	1.3	0.4
Perfluorooctane sulphonate (ng/ml)					
2	424	5.1	3.3	4.4	3.9
4	632	4.4	2.0	4.0	2.5
6[a]	180	3.8	1.4	3.7	2.3
Perfluorooctanoic acid (ng/ml)					
2	424	4.7	3.0	4.0	3.6
4	632	3.9	1.8	3.6	2.0
6[a]	180	3.7	1.6	3.5	1.8

[a]Data for 6-year-old children are yet to be completed. Complete data will be released in mid-2018 after data cleaning.

built-in internal quality controls was assessed using the GenomeStudio Methylation Module (Illumina Inc., San Diego, USA).

All data were collected and managed using the Korea Food and Drug Administration Monitoring Information Management System. Each year, the data were periodically cleaned to address inaccurate or missing values. To obtain the correct values for these data, we either contacted the participants via telephone or conducted an additional survey. Educational and training programmes were provided annually to all survey staff, to maintain consistency across follow-up surveys and improve the data quality.

What has it found? Key findings and publications

Table 3 shows the levels of various environmental pollutants measured from children's urine and blood samples. In general, these levels were comparable to those obtained by previous studies conducted in the Republic of Korea.[12,28–32] The EDC study is still ongoing, and 14 studies whose main results and abstract have been submitted to the scientific research committee have been approved by the committee and were published[13,33,34] or are being processed for publication.

The analysis of the relationship between prenatal urinary concentrations of bisphenol A, which is a ubiquitous endocrine–disrupting chemical, and children's blood pressure at 4 years of age revealed a nonlinear association between these variables. Prenatal bisphenol A levels were positively associated with diastolic blood pressure only above the threshold bisphenol A levels (4.5 μg/g creatinine). However, no evidence was found on the association between prenatal bisphenol A levels and systolic blood pressure.[33]

Phthalates are widely used as plasticizers and solvents, which are known to have endocrine–disrupting effects.[35] The urinary phthalate metabolite levels measured from children's urine were associated with lower IQ and continuous performance test (CPT) scores, an indicator of attentional performance. However, phthalate metabolite levels in the prenatal period were not associated with IQ or attentional performance, suggesting that the postnatal period might be the susceptible period for the development of these neurobehavioural outcomes secondary to phthalate exposure.[34]

The analysis of the associations between prenatal and early childhood bisphenol A levels and social impairment of children at 4 years of age showed that prenatal bisphenol A levels were associated with increased social impairment above the threshold bisphenol A levels (3.0 μg/g creatinine). In contrast, no association was observed between bisphenol A levels in early childhood and social impairment.[13]

Considering that investigation of the possibility of genome-wide DNA methylation profile as the underlying basis for the lasting effects of environmental exposure is one of the main goals of the EDC study, we plan to evaluate the association between environmental exposure and DNA methylation profile and the mediation effect of DNA methylation on the association between environmental exposure and various health outcomes. We expect that the EDC cohort study will provide up-to-date information on the different physical and neurobehavioural developmental trajectories associated with various environmental risk factors and underlying mechanisms behind these associations.

What are the main strengths and weaknesses?

Prospective cohort studies in the field of perinatal and paediatric epidemiology are warranted to reduce the effect of methodological problems, including temporal ambiguity and information bias.[36] The EDC study is a prospective children's cohort study that has several strengths. First, we have incorporated a multimodal approach in contacting participants, which resulted in a relatively high follow-up rate of >80% among 4-year-old children. Considering that follow-up loss could induce substantial bias, especially in cohort studies that explore the adverse effects of environmental exposure,[37] the high follow-up rate in this study is notable. Second, the EDC study is an interdisciplinary study that involves environmental epidemiologists (environmental health centre), nutritionists (environmental health centre), paediatric endocrinologists (growth and developmental assessment clinic), and paediatric psychiatrists (neurobehavioural assessment team) (Figure 2). We have investigated the associations between various environmental risk factors and childhood development in terms of physical and neurobehavioural aspects, which were assessed by medical specialists affiliated with our study. Third, the EDC study analyses the potential of genome-wide DNA methylation as the underlying mechanism behind the different developmental trajectories among children. Although this issue is an important topic that has attracted global attention, only a limited number of cohort studies have investigated the role of epigenetic processes.[8–10]

However, the EDC study has several weaknesses to consider when interpreting the results. The EDC study recruited voluntary participants mainly from the Seoul and Gyeonggi province (metropolitan area) and tended to

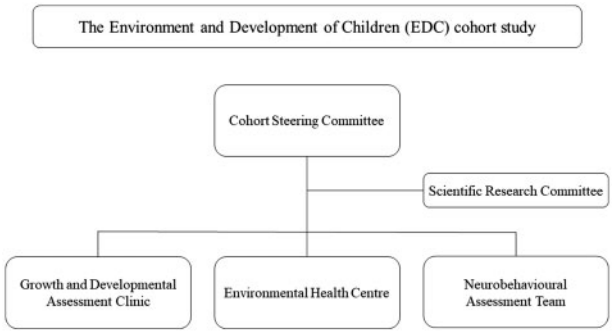

Figure 2. Organizational structure of the Environment and Development of Children (EDC) study.

include individuals with relatively better health status and higher socioeconomic status. We plan to follow up the participating children until they reach 12 years of age. However, maintaining the EDC cohort until the children become adults is more desirable so that the potential long-term effects of environmental exposure, such as the development of non-communicable disease phenotypes, can be assessed. This study analyses genome-wide DNA methylation using blood samples collected from children at 6 years of age. However, the DNA methylation status can change over time in response to various environmental exposures. Therefore, prenatal maternal and paediatric blood collection may be needed to assess the changes in the DNA methylation profiles over time which are associated with environmental risk factors. Finally, further assessment of environmental pollutants, such as polybrominated diphenyl ethers and nanoparticles, would have public health implications given the extensive use of these agents in consumer products and their potential effects on neurodevelopmental and metabolic outcomes.[38,39]

Can I get hold of the data? Where can I find out more?

The high follow-up rate, comprehensive and thorough developmental assessment by medical specialists, and genome-wide DNA methylation analysis in the EDC study provide a unique opportunity to investigate the potential lasting effects of early environmental exposures on the physical and neurobehavioural developments of children. Investigators who are interested in exploring the possibility of collaborations, using the data, and obtaining further information about the EDC study can contact the principal investigator, Professor Yun-Chul Hong [ychong1@snu.ac.kr]. All suggestions will be reviewed by the scientific research committee of the EDC study.

Profile in a nutshell

- The EDC study is a prospective children's cohort study that was conducted to investigate the associations between environmental risk factors and physical and neurobehavioural developments, as well as the mechanisms underlying these associations, particularly with regard to epigenetic processes.
- The EDC participants were recruited from the Congenital Anomaly Study, which enrolled pregnant women between 2008 and 2010. A total of 723 children, mostly residing in Seoul and Gyeonggi province, Republic of Korea, and who were 2–4 years of age, were recruited between 2012 and 2015.
- We conducted follow-up surveys with 2-year intervals. A total of 80.9% of the children who were enrolled at 2 years of age (n = 425) were followed up at 4 years of age.
- The EDC data include sociodemographic and lifestyle characteristics and dietary information obtained through structured questionnaires, environmental pollutant levels measured from blood and urine samples, and genome-wide DNA methylation profiles determined using blood samples collected from children at 6 years of age.
- Researchers interested in collaboration should contact the principal investigator, Professor Yun-Chul Hong [ychong1@snu.ac.kr].

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Conflict of interest: None declared.

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