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FOR THE JAPAN ENVIRONMENT AND CHILDREN'S STUDY

REPORT

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NATIONAL INSTITUTE FOR ENVIRONMENTAL STUDIES

JAPAN ENVIRONMENT AND CHILDREN'S STUDY PROGRAMME OFFICE

English

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Executive summary

The International Advisory Board for the Japan Environment and Children's Study (JECS) was held on 2–3 September 2019 at the National Institute for Environmental Studies, Tsukuba, Japan.

A total of 40 people attended the meeting, including members of the International Advisory Board for the Japan Environment and Children's Study (IAB/JECS) and representatives of the National Institute for Environmental Studies (NIES), JECS Programme Office, JECS Regional Centres and JECS Medical Support Centre.

Ten internationally renowned experts were invited to form the IAB/JECS. Prior to the meeting, the JECS fact sheet and protocols of the Main Study and Sub-Cohort Study were distributed to the IAB members. At the IAB/JECS meeting, further details were provided by the JECS representatives and in-depth discussion was undertaken. JECS sought advice from the international experts on the following topics: 1) study protocol, 2) international collaboration and harmonisation and 3) future plans.

The IAB/JECS members praised JECS as an amazing success story in terms of the inception of the study and recruitment of over 100,000 pregnant women and their babies plus approximately 50,000 fathers, in less than 4 years. There is unlimited potential for studies using this cohort to understand the impact of the environment (defined not only as exogenous chemical substances but also as physical conditions, biological agents, socioeconomical factors, diet and lifestyles) on the health and development of children.

The IAB/JECS advised that it would be unjustifiable if JECS did not continue to follow the children past the age of 13. The role of early life exposure (including pre-conceptional exposure) on later life is only just beginning to be explored and there are multigenerational effects that can be traced to early life exposure. It is essential that the time to initiation and completion of puberty be measured. The IAB/JECS also recommended that the mothers and fathers continue to be studied as they age.

The IAB/JECS noted that the study was primed to deliver extraordinary results from a very limited budget. It is essential that the funding is assured, possibly in 5 year increments, so that the most appropriate plans can be made. To meet the full potential of JECS, additional staff are required. The IAB/JECS would recommend approximately twice as many staff, particularly scientists, in the Programme Office.

The IAB/JECS gave advice and recommendations on JECS protocols. These include incorporating newer exposure methodology into the study, additional analytes, further exploration with untargeted analysis, additional health outcomes and consideration of OMICS (including genomics, exposomics, metabolomics, proteomics and lipidomics). Full appreciation and use of the tremendous number of samples and data collected requires an upgrade of the biobank and environmental sample bank. Procurement of a robotic system is essential as a world-class research infrastructure.

In addition, the IAB/JECS recommended that a strategy document be developed to ensure a clear focus. The IAB/JECS advised JECS that not everything has to be measured in each sample. Development of new Sub-Cohorts that focus on the link between questions and what is being measured is advised.

The IAB/JECS advised that there should be multiple opportunities for international scientists to collaborate with JECS scientists, and even to ask their own questions of the platform provided by JECS. The JECS samples and data should be made available to other investigators as soon as possible, albeit in a tightly controlled manner to protect personal information. Study results should be published as rapidly as possible in peer-reviewed international journals. Participation

in the international birth cohort group, which involves France, Germany, Norway, Denmark, China, US and Japan, is to be applauded.

As the IAB/JECS strongly recommended that JECS continues beyond the age of 13, the continuation of this cohort requires enhanced communication approaches, i.e., greater use of social media and the formation of active groups of participants so that they feel a degree of ownership in the study. The IAB/JECS strongly recommended hiring social scientists into the programme. Once the children reach a culturally appropriate age, they should be fully informed and be able to provide consent themselves. All data should be fed back to the participants unless they explicitly refuse to receive it. While there may be no national norms, a participant's individual levels can be viewed in the context of the rest of the cohort.

Advisors

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1 Japan Environment and Children's Study

1.1 Overview

The Japan Environment and Children's Study (JECS) started in 2011 as a national birth cohort study to examine environmental impacts on children's health and development, in order to facilitate better environmental risk management. Specifically, JECS focuses on the effect of exposure to chemical substances during the foetal period and/or in early childhood.

JECS collects outcome and exposure data/biological specimens from expectant mothers and then periodically follows their children until they reach 13 years of age, constituting the main part of the study (Main Study). The Main Study comprises approximately 100,000 pregnant women, their children and the children's fathers (when accessible). In addition, a Sub-Cohort Study, involving 5,000 children randomly selected from the Main Study was also designed to investigate environmental factors and outcome variables more thoroughly, including home visits, ambient air measurements, psycho-developmental tests and paediatricians' examination. A Pilot Study to evaluate the feasibility, acceptability and cost of the proposed procedures and processes to be used in the Main Study was conducted. In addition, Adjunct Studies are conducted with extramural funding.

JECS is conducted in cooperation with several research institutions. The JECS Programme Office, which is situated in the National Institute for Environmental Studies (NIES), takes a directive role, being responsible for planning the study, preparing standard operating procedures (SOPs) and storing collected data and biospecimens. The Programme office is currently run by 45 staff members. The Medical Support Centre, which is organised within the National Centre for Child Health and Development, supports the Programme Office by providing medical expertise. The Programme Office and Medical Support Centre cooperate with 15 Regional Centres that are located in universities and other research institutions throughout Japan. The Regional Centres are responsible for recruiting and maintaining study participants and gathering data in their selected areas at each study phase.

Priority JECS outcomes include reproduction and pregnancy complications, congenital anomalies, neuropsychiatric and developmental disorders, allergy and immune system disorders, metabolic and endocrine system dysfunction and cancer. Regarding the assessment of exposure, JECS targets a variety of exposures, including chemicals from the environment and occupation, the physical environment, lifestyle and socio-economic status. Genetic and other OMICS factors will also be investigated.

By March 2014, recruitment of participants (pregnant women) into the Main Study was completed. A total of 103,097 mothers were registered, resulting in 100,103 births; 51,909 fathers were registered. Each participant completed a questionnaire twice during pregnancy, at birth and then when the baby reached 1 month and 6 months of age plus every 6 months thereafter. More than 5,000,000 tubes of biological samples have been collected. The Sub-Cohort Study started in November 2014. JECS funding for the fiscal year 2019 is 5.9 billion yen (54 million US dollars). The questionnaire response rate at the age of 7 years was 76.7% and at first grade was 78.0%. As of 1 August 2019, a total of 64 papers have been published from the JECS data, covering subjects such as the association between maternal smoking during pregnancy and birth weight (Suzuki K, et al. [2016] J Epidemiol), metallic elements in maternal blood (Nakayama SF, et al. [2019] J Exp Sci & Env Epidemiol), and the association between Cd and early preterm birth (Tsuji M, et al. [2018] Env Res). Some papers have also been published as a result of international collaborations between JECS and other cohort studies in the Environment and Child Health International Birth Cohort Group (Nakayama SF, et al. [2019]

Int J Hygiene Environ Health).

1.2 Discussion

The following comments and recommendations were made during the discussion:

- Acknowledgement of the success and the importance of continuing the study
  - IAB members congratulated the JECS' success in recruiting > 100,000 women in less than 4 years and maintaining a good follow-up rate.
  - This study should not stop at age 13 because the data are too important. A prospective study is very important to determine early environmental exposure on health in later life and puberty is an important time of life. The availability of electronic health records means that there is no reason to discontinue.
  - JECS is an extraordinary study and is an internationally renowned project; it is the leading birth cohort study in Asia and around the world. JECS is one of very few highly organised epidemiologic studies and it would be disastrous to terminate participation at the age of 13 years.
  - Similar studies, such as the Ko-CHENS study in South Korea, are being developed and will introduce advanced methods for conducting challenging research. We look forward to the ongoing success of JECS and discontinuing follow-up at 13 years of age would limit the role of JECS. JECS should continue at least through adolescence, taking into account the impact through puberty.
- Priorities of the study and use in risk assessment/risk management
  - The productivity of the study is a key reason to support an extension beyond the age of 13 years. A strategic approach and prioritization are key to optimising the study.
  - In Health Canada and Environment Canada, the utilization of study results in chemical risk assessment and risk management has provided the most powerful support for continuing such large-scale studies.
  - The Ministry of the Environment is currently considering ways to use the JECS results in risk assessments, but this is still at an early stage. Currently, JECS has focused on hot topics, in the hope of achieving high impact data to demonstrate its importance. However, JECS understands that topics relevant to risk assessment and risk management must also be evaluated.
  - Issues on mixture effects have become important, and risk assessment of real-life mixed exposure has become a key concern. It is important to see what the real-life mixture in Japan is and JECS will be able to provide valuable data.
  - Prevention of chemical exposure is important.
  - Using the JECS data, particularly exposure levels of hazardous chemicals, policymakers can establish legislation/rules to protect children and pregnant women, particularly those in high exposure groups.
  - Societal interest in chemical risk has declined compared with other environmental topics, such as climate change. However, the health risk caused by chemical substances remains an issue and it is important to have a forefront project like JECS for reference.

  - It is important to have as much data as possible published in scientific journals.
  - The main protocol states that JECS aims to study chemical exposure and children's health. It is recommended that JECS be expanded to include dietary effects, such as nutritional biomarkers. JECS currently has information on food intake via a food questionnaire.

- Sample preservation
  - The samples collected by JECS are invaluable and could be utilised in many future studies. All collected samples must be well preserved and precise data relating to every sample taken will be maintained.

- Budget and staffing
  - Although JECS is planned to continue until the age of 13, the programme must negotiate with the Ministry of Finance for funding annually. It will be difficult to plan the study without knowing how much funding will be secured each year.
  - JECS is surprisingly economical, being able to produce so much data with only the equivalent of 54 million US dollars per year. The ECHO programme in the US costs 160 million dollars per year. It was suggested that the Ministry support the study with additional budget.
  - The study is significantly understaffed; this ambitious study requires twice as many staff to fully accomplish its goals. The Ministry of the Environment should provide more support for staffing.

- The nature of IAB/JECS
  - JECS is still at an exploratory stage. Although the future continuation of the IAB is the NIES's institutional decision, the current meeting was welcomed. Having an expert meeting dedicated to discussion of JECS allows focused, in-depth review. The continuation of such a meeting is supported.
  - As the IAB/JECS is part of the NIES IAB, the focus was on topics relevant to the NIES. In the future, presentations not only from the Programme Office on the Main Study and the Sub-Cohort study, but also from the Regional Centres and Medical Support Centre, as well as presentations on Adjunct Studies would be welcomed. The IAB meeting may also be used as an opportunity for capacity building and training for young researchers, e.g., giving them an opportunity to present their work as posters.
  - More could be done if the information presented at the meeting could be shared in advance.
  - It is important to have a permanent advisory committee but a face-to-face meeting may not always be necessary; for example, important strategic documents could be reviewed by the members online to assist with decision making.

1.3 Recommendations

JECS is an amazing success story considering the inception of the study and the recruitment of >100,000 pregnant women and their babies, as well as 50,000 fathers, in less than 4 years.

This is a nationally representative, longitudinal birth cohort, with 15 regional centres throughout Japan. The program office is located at the NIES and involves 45 people, including the fellows and junior scientists. The study has obtained blood samples at several points during pregnancy, urine samples, cord blood at birth, and multiple biospecimens from the children. Detailed questionnaires are taken at several time points. There is a randomly selected Sub-Cohort of 5000 children who are being followed in greater depth with medical examinations, biological and environmental sampling and questionnaires. The potential for studies using this cohort to understand the impact of the environment (defined not only as chemicals, but also as social factors, diet, infectious agents, etc.) on the health of children is unlimited. It would be a severely missed opportunity not to continue to follow the children past the age of 13 years. The role that early life exposure (including pre-conceptional exposure) has on the entire lifespan is only just beginning to be explored. We do know that there are multigenerational effects that can be traced to early life exposure. It is essential that the time to the initiation and completion of puberty is also measured. In addition, the fertility of those exposed in utero and in early life needs to be examined, as well as their reproductive history. While the number of children may make detection of cancer difficult, this may not be the case when dealing with the children once they reach adulthood. Also, chronic, non-communicable diseases, such as heart disease and type 2 diabetes, can be examined at that time. We would also recommend that the mothers and fathers continue to be studied as they age, as their earlier exposures will be well documented.

This study is primed to deliver extraordinary results from a very limited budget. It is essential that the funding is assured, possibly in 5 year increments, so that long-term plans can be made in advance. This study would also benefit from a high-profile champion who will increase the visibility and importance of this study to the Japanese public. This would also encourage participation in the study to remain high as the children get older.

2 JECS protocol

2.1 Main Study and Sub-Cohort protocols and current status

The JECS Main Study consists of 100,000 participants. Biological samples are collected from the mothers, children and fathers. Questionnaires are administered during pregnancy, at birth, when the baby is 1 and 6 months and every 6 months thereafter until the children reach 13 years of age. Medical records, resident registry and school records are collected. As of July 2019, 103,095 mothers, 100,323 children and 51,908 fathers have been recruited and 95,595 children have been followed-up. Health outcomes are collected through questionnaires and include questions on congenital anomalies, neuropsychiatric development and the immune and metabolic/endocrine systems. Questionnaires are also used to collect information on exposure measurements (chemicals, indoor air pollutants, noise, other pollutants and allergens) and covariates and confounders (parents and children). Blood and urine were collected from mothers (early pregnancy, mid-late pregnancy and at birth) and fathers (ad libitum). Breast milk (1 month) and hair (at birth) were collected from mothers, and cord blood, blood spot (1 month) and hair (1 month) were collected from children. Mid-late term maternal blood has been analysed for metallic elements (Hg, Pb, Cd, Mn and Se) and perfluoroalkyl substances, and early term maternal urine has been analysed for cotinine, 8-OHdG, organophosphate pesticide metabolites (DAP) and environmental phenols (parabens, bisphenols, triclosan, etc.). Analysis of mid-late term maternal urine for phthalates and neonicotinoid pesticides is ongoing.

The Sub-Cohort Study consists of 5,000 participants randomly extracted from the Main

Study. The Sub-Cohort Study includes a home visit to inspect the dwelling, examine indoor and outdoor air quality, particulate matter, house dust and noise when the children are 1.5 and 3 years of age. Psychological development testing, physical examination, blood and urine collection are performed at 2, 4, 6, 8, 10 and 12 years of age. Developmental tests were undertaken using the Kyoto Scale of Psychological Development at the age of 2 and 4 years and a computer-assisted testing system at the age of 8 years. Medical examinations (including physical measurement, blood tests and visual examination of the skin) are performed at the age of 2, 4, 6, 8, 10 and 12 years. Exhaled NO and spirometry are also assessed at 8 years. Blood samples will be examined for chemical substances and health biomarkers, including antibodies (non-specific IgE, specific IgE, IgA, IgG1 and IgG4, and measles antibody), thyroid hormones (TSH, FT4, T4, T3 and fT3), 25(OH)Vitamin D, IGF-1, LH, FSH, steroid hormones, HbA1c, glucose, insulin, LDL, HDL and TG.

School age examination is planned for the whole cohort, i.e., 100,000 participants. Second grade examination (at 8 years) started in July 2019 and physical examination, developmental testing using a computer assisted testing system and urine collection is performed.

Tools for the exposure assessment include biomonitoring (blood, urine, milk and hair), environmental measurement, questionnaires and modelling. Analysis of various chemicals and biochemical markers is planned for all samples (Main Study) or smaller samples (Sub-Cohort study and nested studies), depending on the chemical. Analytical methods have been developed for blood (metals [Cd, Hg, Pb, Mn and Se], perfluoroalkyl and polyfluoroalkyl substances [PFAS], and Me-Hg) and urine (cotinine, 8OHdG, phenols [parabens, bisphenols, etc.] and organophosphate metabolites) and have already been applied to maternal blood, urine and cord blood samples. Method development for persistent organic pollutants (POPs) and dioxins (aryl hydrocarbon receptor active compounds) in blood and pyrethroid metabolites and arsenic speciation in urine are under way, and method development for the detection of phthalates and neonicotinoids in urine is near completion. Use of wearable sensors and samplers is currently being explored. Tooth analysis is also under consideration. Environmental measurements are performed in the Sub-Cohort study. For the questionnaire component, because no standardised questionnaire for exposure assessment exists, JECS is trying to develop its own. For modelling, various approaches are being explored, including inverse distance weighting interpolation, a land use regression model, satellite image/data, built environment, greenness and pharmacokinetic modelling.

2.2 Discussion

The following comments and recommendations were made during the discussion:

- Target chemicals and sample analysis
  - A strategic approach is necessary to accomplish the objectives of the study.
  - Not all target chemicals need to be analysed from the entire cohort. For example, traditional POPs may be reduced in numbers. New chemicals of interest will continue to emerge and having too many samples to analyse will slow the process.
  - Analysis of sample size is required. The necessary sample size will differ according to the study objective (e.g., the difference between regions of Japan). To look at secular trends, repeated cross-sectional studies are required and not repeated measures of the birth cohort.

  - Efforts to measure 28 PFAS are good, but there are more than 500 related chemicals and there is no way to measure all of them. In addition, we may be exposed to classes of chemicals that have not been considered. Untargeted analysis could be a way forward.
  - Identifying the known effects of certain chemicals will prove the validity of the study, which is also useful to demonstrate the importance of the study to funding sources and policy makers. At the same time, it is also important to investigate the effects of chemicals that have not been identified. The volume of biological samples is limited. Ko-CHENS is working to develop a method of analysing various substances simultaneously using only a small volume. However, we may not be able to analyse as many chemicals as we would like. Therefore, it is necessary to use non-target screening analysis.
  - JECS could create a 'discovery cohort' to perform untargeted analysis in a portion of the cohort to prioritise key chemicals; an appropriate methodology for this untargeted analysis is being developed.
  - With the first exposure results available, the addition of a new Sub-Cohort may be an option. For instance, a Sub-Cohort study could be performed for mercury to find the threshold for this heavy metal. Mercury in blood samples could be studied through self-reported information on fish consumption. A carefully selected Sub-Cohort that covers a wide range of exposure could provide answers to such questions and social needs and trigger a new hypothesis.
  - Nested case-control studies could be performed and JECS can utilise larger sample sizes to test the hypothesis.
  - Collaboration with other laboratories/institutions may reduce the JECS workload and improve productivity. For example, other laboratories may already have established methodologies for certain chemicals and could perform routine analysis.
  - JECS should follow up on the developments in the chemical market and determine shifts in the use of certain chemicals. JECS will be able to follow the effects of chemical regulations and such information will be important for the government. For example, Germany has monitored DINCH. JECS has analysed DINCH in samples collected in 2011–2014 and in the pilot study collected 2 years earlier, but DINCH was not detected.
  - JECS is currently trying to automate the analysis procedure to reduce sample use and human handling; contract laboratories are used to analyse the target chemicals from the samples.
  - JECS contains a state-of-the-art biomonitoring programme, including miniaturisation of sample analyses.
  - JECS could add new chemicals, such as alternative flame retardants, to its target chemicals.
  - Studies on non-persistent chemicals are normally conducted for only one or two time points. JECS could perform such studies at three or more points to identify the critical window of time.

- Biobank

  - Methods for measuring environmental exposure, including biological sample analysis, have been continuously improved and new methods have been proposed. Therefore, it would be better to construct a more flexible organisation in promoting research.
  - A more careful approach is needed when utilising biological samples from long-term storage. It requires a new and separate facility, including an automated biobank and research facility.
  - A solid biobank is one of the most important aspects of a birth cohort study.

- Urine samples must be interpreted with care, as a urine sample only represents a single point in time; if the exposure comes from food, it will only be high after food consumption. There is a lot of research variation between different urine measures. However, urine sampling must also be feasible in the field. Because JECS has a large sample size, urine measurements are able to represent the general Japanese population well.

- JECS has the largest collection of breast milk samples to date. There are other studies, but these date back to 20 years ago and the sample size is limited. JECS will analyse the breast milk samples and has plans for pharmacokinetic modelling to predict and assess blood concentrations of chemicals in children from breast milk.

- Personal monitoring

  - In the USA, giving out personal samplers to children in the form of colourful wrist bands has been successful and seemed to be a better measure of exposure. House dust is also a very rich source of identifying exposure, particularly when we consider the length of time that people are staying indoors.
  - Questions about how the children are raised could be included in the questionnaire to find out, for instance, how the children spend their days, or if the child goes to childcare centres. This would provide a better understand of their exposure.

- Epigenetics, genetics and metabolomics

  - A genome-wide association study for all complete trios (mother, father and child) is recommended; this will increase participation in international studies.
  - JECS should include epigenetic analysis.
  - At the time JECS received consent from the participants, details of the genetic analysis had not been decided. JECS is currently planning genetic analysis and determining how to inform the participants to obtain consent if it needs to be renewed.
  - The microbiome of children should be evaluated along with nutritional information as we are starting to understand how important the microbiome is to our health. Such studies should be considered at ages 8, 10 and 12 years.
  - JECS should seriously consider performing metabolomics in a small sample group in a discovery manner. Looking for some biomarkers of response from metabolomics may be a way forward.

- Investigation of puberty

  - Investigation of puberty, particularly the progression of puberty, is valuable. The IAB/JECS recommends that JECS extend the duration of the study to cover the entire lifespan.
  - In JECS, the method of pubertal assessment is under discussion. The current idea is to use a questionnaire because of the difficulties associated, e.g. ethical boundaries, with including it in the medical assessment.
  - Clinical assessment will be valuable. Self-reports could be used for onset and completion of puberty, but not for progression. Obesity and physical activity affect puberty, so these should also be considered.
  - Using the Tanner scale may be an option. However, there are potential cultural issues associated with its use and working with a social scientist may be helpful. For example, in Germany, the Tanner scale could not be used because 50% of the children shaved their hair.

- Parental health
  - JECS currently does not plan to take further biological samples from mothers or fathers. It is important to look not only at the children's health, but that of their parents as well.
  - It may be interesting to go back to the fathers and look at the epigenetics of their sperm, for example, in a Sub-Cohort analysis. In mothers, analysing any association with menopause may be an option.

- More focus on aetiology and health outcomes
  - There are two main reasons to undertake such an exposure study. One is to understand the exposure and the other is aetiology. There is value in measuring exposure, but society's interest has moved more toward their effects on learning abilities or the immune status of children, for example.
  - JECS has the potential for aetiological assessment. JECS should place a greater priority on health outcomes and be clearer on this topic.
  - JECS could contribute to wider society by analysing connections with disease and communicating key approaches to preventing such health risks.

- JECS organisation
  - JECS does not have a medical or toxicology group in the governing body and committees. As there are many outcomes to evaluate, a group tasked to look at the outcomes may be required.
  - JECS will need to be pragmatic about organising committees. In the Norwegian Mother, Father and Child Cohort Study (MoBa), ad-hoc meetings to discuss certain topics have been helpful.

- JECS has a large Fukushima prefecture cohort; the study does not currently plan to analyse the effects of the earthquake, but such studies are recommended.

- Other items that should be considered by JECS

  - Determine the effects on the immune system in more detail. Autoimmune diseases and rheumatoid arthritis could be added.
  - Consider incorporating hearing tests as they are relatively easy to implement and there have been reports of chemical exposure being associated with hearing problems.
  - Mental health, depression and anxiety, which are common in adolescence, could be evaluated along with the role of social media.
  - Consider analysing exposure from drinking water as many of the target compounds are also found in this source. Samples could be collected at the age of 8 years at home visits.
  - Assess dietary intake as much as possible. Pictures of food may be useful for keeping track of the diet.
  - JECS should consider analysing urinary fluoride as this could come from water, toothpaste, mouthwash and so on.

- IAB/JECS does not expect JECS to do all the above independently, and these ideas could be accomplished through collaboration with other groups.

- A strategy document should be prepared to help clarify the study's focus and aims.

2.3 Recommendations

JECS is advised to incorporate newer exposure methodology into the study. Examples include: the use of silicone wristbands for integrated personal exposure; use of smartphones to measure activity and take pictures of the diet; and the use of baby teeth to enable retrospective exposure assessment and assessment of windows of susceptibility.

For urine samples, it is unclear when/how the urine samples are being collected. For some contaminants with a short half-life in humans, multiple specimens must be taken, particularly if the timing of critical sensitivity is still unknown. The house dust should be examined further in addition to moulds and allergens. House dust (or dust at a day-care centre or school if that is where the child spends his/her time) is a major source of chemical exposure. In addition, tap water should be sampled from the home as the content of water may be as important as the dust or air.

JECS should consider measuring additional analytes, particularly those that were not of concern 10 years ago, over legacy compounds. Examples include metabolites of organophosphate flame retardants, chlorinated paraffins, replacement brominated flame retardants and many more PFAS. Urinary fluorides should be measured. JECS is advised that not everything must be measured in each sample. New Sub-Cohorts should be developed to focus on the link between the question and what is being measured.

In reality, exposure is likely to be a complex mixture. It is extremely important that untargeted analyses be conducted and that OMICS, including exposomics, metabolomics, proteomics and lipidomics analysis, are examined.

JECS is advised to look at the effects on the immune system in more detail. Examples include the incidence of infectious diseases and the success of vaccination for diphtheria and tetanus. An approach similar to that used in the Hokkaido Study on Environment and Children's Health could be used. The incidence of Type-1 diabetes and other autoimmune disorders should be studied

and key cytokines should be measured. Corticosteroid levels in the blood may be evaluated as a simple measure of stress. It may be too late to measure corticosteroid levels in the mothers, but a Sub-Cohort of children would be possible.

Other additional health outcomes that JECS should consider measuring include hearing levels in the children, kidney function, liver function, and the initiation, duration and completion of puberty. For the assessment of liver function, there are more sensitive measures today than those currently planned by JECS. Cytokeratin 18, which can discriminate between necrosis and apoptosis, should be considered. For puberty, use of the Tanner scale for both boys and girls should be considered. The epigenome should be examined at multiple time points in the study. Samples of the faecal microbiome should be obtained from the children at the age of 8 years and then also after they reach puberty. This can also clearly demonstrate the impact of the diet, as well as modulating the effects of environmental exposure.

Fukushima presents an important opportunity, not only to look at the effects of radiation and flooding, but to look at the long-term effects of a disaster on the population. This should also focus on mental health issues.

3 International collaboration and harmonisation

3.1 Discussion

International collaboration and harmonisation were discussed and the following comments and recommendations were made:

- Some methodologies have already been developed by other laboratories. Collaboration with other laboratories, particularly those who routinely undertake such analysis, will lighten the workload. Such collaboration may also lead to additional funding from other finance sources.

- Partnering with Germany and Canada who have experience in human biomonitoring and networks such as HBM4EU may be helpful.

- Untargeted screening is an opportunity for international collaboration.

- JECS' collaboration with external researchers, such as the Karolinska Institute, is currently focused on method development.

- JECS is unable to share biological samples with external researchers due to technical and procedural limitations. Procurement of a robotic system is necessary to prepare the samples and JECS does not yet have a framework to share samples and data, even in domestic collaboration. JECS is still discussing how sample and data sharing could be achieved. In addition, the personal information protection act had been revised and there is a need to comply with the new rules.

- The mood in the scientific community is for transparency. Limited access to the samples and data may limit opportunities for collaboration.

- International collaboration is essential, particularly to publish results on genetics.

- Regarding childhood cancers, none of the cohorts can work independently and MoBa, the Danish National Birth Cohort (DNBC) and JECS could work together. Diet during pregnancy and childhood cancer could be obvious areas for collaboration.
- Quality assurance and quality control systems are recommended.
- Harmonization is not always necessary.
- There are ways to collaborate without transferring data or samples. DataSHIELD is a platform used in Europe. In MoBa and DNBC, remote access to data is given and all analysis can be performed on the secure server.
- JECS should aim to work towards multilateral agreements to obtain funding for international collaborations.
- External applicants could use multiple principal investigators.
- Procedure for manuscript submission
  - Six weeks is required for internal approval before manuscript submission. This procedure was established to check the quality of the publication and to avoid duplicate publications.
  - MoBa has reduced the bureaucracy regarding manuscript submission. For example, MoBa first had exclusivity for PhD students but this was subsequently abolished. MoBa has also decided not to check the scientific quality of the paper as it will be reviewed by the individual scientific journals.
  - JECS should have a graphic presentation of the steps necessary for data analysis and manuscript submission on their website for future collaboration.
- JECS should publish their results in international, English language journals as much as possible.
- JECS has put a lot of effort into harmonising international cooperation and analytical methods. In the future, new research cooperation is required relating to analysis methods using new biomarkers.

3.2 Recommendations

JECS has achieved worldwide recognition and admiration. There should be multiple opportunities for international scientists to collaborate with JECS scientists, and to ask their own questions using the platform provided by JECS. The JECS samples and data should be made available to other investigators as soon as possible, although this will be done in a tightly controlled manner. Peer-reviewed publication of studies should be completed as quickly as possible in international journals.

JECS is one of the four largest birth cohorts in the world and there should be attempts to harmonise the methodology when appropriate. JECS is more current than MoBa or DNBC.

Participation in the international birth cohort groups, which involve France, Germany, Norway, Denmark, China, US and Japan, is to be applauded.

4 Future plans

4.1 Upcoming protocols

Self-administered questionnaires for children are planned at the age of 10, 11 and 12 years. A leaflet explaining the content of the research will be distributed with the questionnaire. Developmental testing (Continuous Performance Test, Mental Number Line, Dimensional Change Card Sorting Test, Finger Tapping Test) is planned at the age of 8 and 12, and WISC-IV is under consideration for participants aged 10 years. Physical measurements, blood test and visual examination will be continued and performed at the age of 2, 4, 6, 8, 10 and 12 years. Biomonitoring items from the blood test beyond the age of 10 are still under consideration. Exhaled NO and spirometry are planned at the age of 8 years and examinations for puberty and microbiome are under consideration. A sixth grade examination is scheduled for 2023–2026, which will include a physical examination, developmental test and collection of blood and urine.

4.2 Discussion

The following comments and recommendations were made during the discussion:

- There is no scientific reason to not continue the study beyond the age of 13 and to cover their life span. In fact, it would be ideal if the participants could be followed for three generations. To not follow up the parents would also be a missed opportunity.
- It is very important to investigate the effects of chemicals in adolescence. JECS needs to be extended to adolescence given the impact on future generations. Since there is a limited biomonitoring programme in Japan, which only involves an adult population, JECS comprises an important part of the biomonitoring of women of child-bearing age, foetuses, infants and children. It is expected that the JECS data will contribute to establishing hazardous substance management policies. If extended beyond adolescence, JECS will play a very important role as a means of obtaining information on the exposure of hazardous substances and health effects in the next generation, and to better understand social problems in Japan, such as low fertility and ageing.
- JECS could use computer games for cognitive testing.
- JECS could use short smartphone questionnaires for children. In DNBC, the questionnaires become shorter as they develop. Children could be asked to complete dietary intake questions.
- Behavioural science is necessary to understand what is going on in puberty, adolescence and young adulthood.
- Communication with participants
  - It is important to optimise contacts with children and families to increase participation and minimise attrition. The use of communications platforms that are currently popular among children would be effective. JECS should involve social scientists in the development of such materials.
  - Beyond the age of 10 years, JECS could involve the children themselves in the development of communications materials.

- Returning results to participants
  - JECS has reported results (numbers and some interpretation) to the participants. The data interpretation is limited as Japan does not have indices equivalent to the German HBM values.
  - In Germany and Europe, the participant's desire to know their own exposure level is a part of their motivation to participate in the study. JECS has received no responses (positive or negative) from the participants yet.
  - All data should be provided to the participants unless they decline. In the US, schematic, cohort values are shown, and the participant's individual value is mapped so that they can see how their exposure level compares to the rest of the cohort.
  - Regarding unexpected findings, JECS has criteria for Thyroid hormones and Vitamin D. The criteria for genetics findings are under discussion. The study does not have guidelines for chemical measurements, and this is dealt with case by case. For example, there was a participant with a high Se concentration and JECS liaised with this individual to determine what had caused such high exposure.
- Cohort maintenance
  - Cohort maintenance is important and increasing the identity of the participant as part of a unique study is key. JECS should consider making communication to children a higher priority, particularly if it is hoping to continue the relationship beyond the age of 13.
  - The US was unable to establish a national children's study and with the cooperation of numerous cohorts is now trying to create a synthetic cohort (the ECHO programme). Through the ECHO programme, we have learned that communication is essential. To keep people together and maintain interest in the program, we have arranged for participating children to play together. It is important to increase interest and encourage participants to take ownership of their data.
  - Utilisation of social media may be an option. For example, DNBC used Facebook and famous YouTubers to encourage children to complete questionnaires. DNBC also had some children as ambassador representatives to appear in videos and to encourage others to participate.
- Outreach activities
  - Outreach to the general public is important to keep JECS running.
  - In Canada, it is common to create a summary of the studies as an outreach material. In JECS, the Ministry of Environment holds an annual symposium to inform the public about JECS progress. In addition, when each research paper is accepted in scientific journals, the authors must submit a Japanese abstract when reporting the acceptance to the Ministry of Environment. The authors are encouraged to write these in a way that is easy to read and they are available on the web. In addition, once the paper is accepted, the regional centres will issue a press release.
  - Publication of synthesis reports for other scientists is also recommended.
  - JECS results must be shared with stakeholders to help minimise the wider chemical exposure risk to society.

  - JECS should also provide materials that could be used by the Ministry of Environment to effectively communicate the importance of the study to the public.
  - Currently, JECS does not employ any social scientists. Regional Centres are responsible for communicating with participants and the programme office generates videos and materials that they can use. JECS also does not have social networking service accounts.

- JECS should have social scientists to work on the translation of results, policy implications and communications.

4.3 Recommendations

As discussed in the overall comments and recommendations, there is every scientific reason to continue JECS beyond the age of 13 years. Much of the promise of the study would be lost if the children are not followed into adulthood and, hopefully, into the third generation. Not only should Sub-Cohort studies be utilised, but nested studies are key.

Full appreciation and use of the tremendous number of samples and data requires an upgrade of the biobank and environmental sample bank. Procurement of a robotic system is essential as an advanced data management system.

Continuation of this cohort requires enhanced communication approaches, including greater use of social media and the formation of active participant groups that will foster a feeling of ownership in the study. The IAB/JECS strongly recommends that social scientists be hired into the programme.

Given the study's intention to continue observation of the children as they mature into adults, an appropriate age should be determined at which the subjects can give their own informed consent.

All data should be fed back to the participants unless they explicitly refuse to receive it. While there may be no national norms, a participant's individual levels can be placed in the context of the rest of the cohort.

To meet the full potential of JECS, additional staff are required and the IAB/JECS would recommend approximately twice as many staff in the program office.

Japan Environment and Children's Study 1-December-2014

International Advisory Board Report Japanese

NIES/IAB/JECS/2019/JP/FINAL
Unclassified

報告書（日本語訳）

国際アドバイザーリーボード会合エコチル調査分科会

2019年9月2日、3日

国立研究開発法人国立環境研究所

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Japanese

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添付資料（英語のみ）

エグゼクティブ・サマリー

2019 年 9 月 2 日、3 日に、茨城県つくば市の国立環境研究所において、国立環境研究所国際アドバイザーリーボード会合エコチル調査分科会（IAB/JECS）が開催された。

本分科会には、IAB/JECS 委員の他、国立環境研究所（NIES）、エコチル調査コアセンター、エコチル調査ユニットセンター、エコチル調査メディカルサポートセンターの代表者を含む合計 40 名が出席した。

委員として、国際的に著名な 10 名の専門家を招聘した。委員には事前に、エコチル調査ファクトシート並びに全体調査及び詳細調査の研究計画書を配布し、エコチル調査に関する詳細な情報を提供した。分科会当日には、エコチル調査の代表者から調査に関する詳細な説明が行われ、調査の細部にわたり議論が行われた。分科会では、1）エコチル調査の研究デザイン、2）国際連携及び国際ハーモナイゼーション、3）将来の計画の 3 つの議題について助言を受けた。

IAB/JECS 委員は、エコチル調査が 10 万人以上の妊婦とその子どもと約 5 万人の父親のリクルートを 4 年足らずで完了し、研究を開始したことは、大変素晴らしい成功例であると称賛するとともに、このコホート研究は、環境（外因性の化学物質だけでなく、物理的条件、生物学的因子、社会経済的要因、食事、ライフスタイルと定義）が子どもの健康と発達に与える影響の解明に役立つ、無限の可能性があると期待を寄せた。

また、エコチル調査が調査対象の子どもを 13 歳以降追跡しないことを正当化する理由は一切ないと助言した。母親の妊娠前をも含む、子どもの成長の初期段階での曝露が、その後の子どもの人生全体に及ぼす影響に関する研究は始まったばかりである。多世代に及ぶ影響の中には、人生の初期段階の曝露に起因する影響も存在することが知られている。また、思春期の開始と終了の両方の把握が不可欠である。さらに、IAB/JECS は、母親と父親についても、引き続き調査対象として追跡することを推奨した。

IAB/JECS は、この調査が非常に限られた予算の中から成果を出すことが強く求められていることを指摘した。最適な計画を立案するには、安定した予算の確保が不可欠であり、おそらく 5 年単位での予算確保が適切である。エコチル調査の可能性を最大限に引き出すには、人員の増強が必要である。IAB/JECS は、コアセンターの人員、特に科学者を増員し、約 2 倍にまで増やすことを推奨した。

IAB/JECS は、エコチル調査研究計画書に関する助言と勧告を行った。勧告には、新しい曝露評価方法の導入、分析対象物質の追加、untarget 分析に関する更なる検討、調査対象健康アウトカムの追加、並びにゲノミクス、エクスポソミクス、メタボロミクス、プロテオミクス、リピドミクス分析を含むオミクス解析の検討等が挙げられた。収集した膨大な試料及びデータを完全に評価し活用するには、バイオバンクと環境試料バンクの改善が必要であり、世界クラスの研究施設としては、ロボットシステムの調達が不可欠である。

さらに、IAB/JECS はエコチル調査が戦略文書を作成し、焦点をより明確化することを推奨した。すべての調査項目をすべての試料で測定する必要はないと助言するとともに、研究課題と測定対象との関連に焦点を当てた新しいサブコホートの設置を推奨した。

IAB/JECS は、国外の科学者がエコチル調査の科学者と協力する機会は複数あるべきであり、エコチル調査が提供するプラットフォーム上で彼ら自身の研究課題についての研究が可能となるべきであると助言した。エコチル調査の試料とデータは、個人情報保護の観点から厳重に管理された方法で、可能な限り早く他の研究者が利用可能にする必要がある。また研究結果は、査読付きの国際誌に可能な限り早く投稿すべきである。フランス、ドイツ、ノルウェー、デンマーク、中国、米国、日本を含む国際出生コホートグループへの参加は称賛される。

IAB/JECS は、エコチル調査が 13 歳以降も継続することを強く推奨しており、コホートの継続には、コミュニケーション手段の強化、例えば、ソーシャルメディアの更なる活用や調査参加者本人が調査に対する当事者意識を持つための活動グループの形成等が必要であると助言した。また、社会科学者の雇用を強く推奨した。子どもが文化的に適切な年齢に達した際には、適切な説明を行った上で、本人から同意を得るべきであり、データの取得を明示的に拒否しない限り、すべてのデータは参加者に返却されるべきである。また、国家的な参照値が存在しなかったとしても、参加者の個々の測定結果がコホート全体に対してどの位置にあるのかを示すことは可能である。

国際アドバイザーリーボード会合エコチル調査分科会委員

Linda Birnbaum (Chair)	National Institute of Environmental Health Sciences and National Toxicology Program, the United States of America
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Michael Borghese	Health Canada, Canada
Ghislaine Bouvier	Bordeaux University, France
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1　子どもと環境に関する全国調査（エコチル調査）

1.1　概要

子どもの健康と環境に関する全国調査（エコチル調査）は、環境が子どもの健康と発達に及ぼす影響について調査し、より適切な環境リスク管理を促進していくために2011 年に開始された全国規模の出生コホート調査である。エコチル調査では、特に胎児期から小児期にかけての化学物質曝露が及ぼす影響に着目している。

エコチル調査では、調査の主要部分（全体調査）として、妊婦をリクルートしアウトカム及び曝露データや生体試料を取得した後、その子どもが 13 歳に達するまで定期的なフォローアップを行っている。全体調査の対象者は、100,000 人の妊婦、その子ども及び子どもの父親（調査可能な場合）である。追加的に、全体調査から無作為に抽出した子ども 5,000 人を対象とした詳細調査を実施している。詳細調査は、訪問調査、環境大気測定、精神神経発達検査、小児科診察等により、環境要因及びアウトカムをより詳細に調べられるように設計している。全体調査で用いる手順や計画の妥当性や実行可能性、費用の検証には、パイロット調査を実施している。さらに、外部資金による追加調査も実施している。

エコチル調査は複数の調査機関の連携のもと実施している。エコチル調査コアセンターは、国立環境研究所（NIES）内に置かれ、標準作業手順書（SOPs）の作成や収集及び採取したデータ及び生体試料の保存等、エコチル調査を統括する役割を担っている。現在、エコチル調査コアセンターは 45 人の職員により運営されている。メディカルサポートセンターは、国立成育医療研究センター内に置かれ、医学的専門知識の提供によりコアセンターを支援している。コアセンター及びメディカルサポートセンターは、全国の大学やその他の研究機関に設立されている 15 のユニットセンターと協働している。ユニットセンターは調査対象者のリクルート及び維持を担当するとともに、各調査段階において調査地域のデータを収集する。

エコチル調査では、妊娠・生殖、先天奇形、精神神経・発達、免疫・アレルギー、代謝・内分泌、がんを主要なアウトカムとして調査している。曝露評価では、エコチル調査では環境及び職場の化学物質、物理的条件、生活スタイル及び社会経済的要因を含む様々な曝露を対象としている。遺伝子やその他オミクス解析についても調査を行う。

2014 年 3 月時点で、全体調査の参加者（妊婦）募集は完了した。母親の登録数は

103,095 人に達し、出生数は 100,323 人であった。父親の登録数は 51,908 人であった。各調査対象者には、妊娠期間中に 2 回、出産時、出生後 1 か月、出生後 6 か月、以後 6 か月毎に質問票による調査が実施される。これまでに 500 万検体を超える生体試料を収集した。詳細調査は 2014 年 11 月から開始した。2019 年度のエコチル調査予算は 59 億円であった。子どもが 7 歳に達した後の質問票の回収率は 76.6% であり、小学 1 年生の回収率は 78.0% であった。

2019 年 8 月 1 日現在､合計 64 報の研究論文がエコチル調査から発表された｡研究論文の例としては､妊娠中の喫煙と出生体重の関連（Suzuki K, et al. (2016) J Epidemiol）や､妊娠女性の血中金属元素濃度（Nakayama SF, et al. (2019) J Exp Sci & Env Epidemiol)､カドミウムと早産の関係（Tsuji M, et al. (2018) Env Res）を調査した研究がある。また、大規模出生コホート調査に関する国際作業グループ（ECHIBCG）におけるエコチル調査と他のコホート調査の国際連携の成果として発表された論文もある（Nakayama SF, et al. (2019) Int J Hygiene Environ Health)。

1.2 討論

分科会では、以下の討論が行われた。

- 調査への称賛と調査継続の重要性
  - エコチル調査が 10 万人を超える妊婦のリクルートを 4 年足らずで完了し、その後も高いフォローアップ率を維持し続けていることは称賛に値する。
  - エコチル調査は極めて重要な調査であり、13 歳で終了させてはならない。前向き研究は、人生の初期段階での環境曝露がその後の健康に及ぼす影響を調査する上で非常に重要であり、また、思春期も大変重要である。医療記録の電子化も進んでおり、調査を終了する理由は存在しない。
  - エコチル調査は世界でも抜きんでた、国際的に有名なプロジェクトであり、アジア及び世界の出生コホート研究をリードする研究の一つである。エコチル調査は、非常に統率の取れた数少ない疫学研究の一つであり、子どもが 13 歳に達した時点で調査を終了することは大きな損失である。
  - 例えば韓国の Ko-CHENS 調査等、同様の研究では、挑戦的な研究の実施及び促進のため、より高度な手法を開発し導入している。我々は、エコチル調査の成功を楽しみにしている。エコチル調査のフォローアップが 13 歳で

終了すれば、エコチル調査の果たせる役割は制限される。思春期の発達への影響を考慮し、少なくとも青年期まではエコチル調査を継続させる必要がある。

- 調査内の優先度及びリスク評価、リスク管理における活用
  - 調査の生産性は、調査を 13 歳以降も延長するための最も強力な根拠の一つとなる。戦略的アプローチと調査内の優先度の整理は、調査を最大限に活用する鍵となる。
  - カナダ保健省とカナダ環境省では、化学物質のリスク評価及びリスク管理への研究結果の活用が、このような大規模研究を継続させる最も強力な理由となっている。
  - エコチル調査の場合、環境省がリスク評価における結果の活用方法の検討を開始したところである。エコチル調査では、世界に大きな影響を与えるデータを成果として公表することが調査の重要性を示すことにつながると考え、今現在多くの関心や興味が持たれているトピックに焦点を当てている。その一方で、エコチル調査は、リスク評価やリスク管理に関するトピックの調査も必要であることを理解している。
  - 複合曝露影響に関する問題が重視されつつあり、現実世界の複合曝露のリスク評価が大きな関心事項となっている。日本の現実世界における複合曝露の把握は重要であり、エコチル調査は貴重なデータを提供できるだろう。
  - 化学物質曝露の未然防止は重要である。
  - エコチル調査のデータ、特に有害化学物質の曝露レベルに関するデータを用いることで、政策立案者は、特に高曝露集団に属する子どもや妊婦を保護する法律や規則の制定が可能となる。
  - 化学物質のリスクに対する社会の関心は、気候変動等の他の環境トピックと比べて低下しつつある。しかし、化学物質による健康リスクは依然として問題であり、エコチル調査のような最先端のプロジェクトが、調査例として示されることが重要である。
  - 可能な限り研究データを科学雑誌で公開することが重要である。
  - 全体調査の研究計画書において、エコチル調査は化学物質の曝露が子どもの健康に与える影響を明らかにすることが目的であると述べているが、エコチル調査を拡張し、栄養バイオマーカー等の食事効果を研究に含めるこ

とを勧める。エコチル調査では、現時点では質問票調査を通じて食物摂取に関する情報を取得している。

- 試料保管
  - エコチル調査が収集した試料は非常に貴重であり、今後多くの研究での活用が期待される。収集したすべての試料を適切に保管するとともに、採取したすべての試料の正確なデータを保持する必要がある。
- 予算と人員配置
  - エコチル調査は 13 歳まで継続予定であるが、本調査の予算獲得には財務省との交渉が毎年必要である。確保できる予算額の見通しが立たない中で研究計画を立てることは困難である。
  - エコチル調査は驚くほど経済的であり、年間わずか 60 億円程度で多くの成果を生み出している。米国の ECHO プログラムの費用は年間約 160 億円である。省庁がより多くの予算を付け、調査を支援することを提案する。
  - 本調査の従事職員数は大幅に不足している。この野心的な研究を完遂するには現在の 2 倍の職員が必要である。環境省は人員配置に関してより多くの支援を与えるべきである。
- IAB/JECS のあり方
  - エコチル調査はまだ探索的な段階にある。IAB の今後の継続は NIES の組織上の判断により決定されるが、IAB/JECS は、現在の IAB 分科会の構成を歓迎する。エコチル調査専用の専門家会議の開催は、エコチル調査に絞った詳細なレビューを可能とする。IAB/JECS は、このような分科会の継続的な開催を支持する。
  - IAB/JECS は NIES IAB の一部であるため、今回の議題は NIES に関連するものに限られた。将来的には、エコチル調査コアセンターからの全体調査及び詳細調査に関する報告だけでなく、ユニットセンターやメディカルサポートセンターからの報告や、追加調査に関する報告も歓迎する。IAB 分科会を若手研究者の能力開発とトレーニングの機会として活用することも可能であり、例えばポスター発表による研究成果発表等が考えられる。
  - 分科会で新たに提示した情報についても、事前に委員と共有することで、更に多くの助言が可能となる。
  - 恒久的なアドバイザリー委員会の設置が重要であるが、対面での会議は必

ずしも必要ではない。例えば、重要な戦略文書を委員がオンラインでレビューし、調査における意思決定を支援することが可能である。

1.3 助言

10 万人以上の妊婦とその子どもと 5 万人の父親のリクルートを 4 年足らずで完了したエコチル調査は大変素晴らしい成功例である。本調査は日本を代表する縦断的出生コホートであり、全国に 15 のユニットセンターがある。エコチル調査コアセンターは NIES にあり、フェローや若手研究者を含む 45 人が従事している。この調査では、妊娠中に数回血液試料を採取し、出生時に臍帯血と尿を採取した後、子どもから複数の生体試料を採取する。また、調査期間中、いくつかの時点で詳細な質問票調査を行う。さらに、無作為に抽出された 5,000 人の子どものサブコホートがあり、健康診断、生体試料及び環境試料の採取、質問票調査で更に詳細な追跡が行われる。このコホートを使用した研究が、環境（化学物質のみならず社会要因、食事、感染因子を含むものとして定義される）が子どもの健康に与える影響の解明につながる可能性は無限にある。子どもたちを 13 歳以降追跡しないことは、貴重な調査機会を逸することになる。母親の妊娠前をも含む、子どもの成長の初期段階での曝露が、その後の子どもの人生全体に及ぼす影響に関する研究は始まったばかりである。多世代に及ぶ影響の中には、人生の初期段階の曝露に起因する影響も存在することが知られている。また、思春期の開始と終了の両方の把握が不可欠である。さらに、子宮内及び幼少期に曝露を受けた者の生殖能力と生殖歴を調査する必要がある。がんについては、子どもの段階では症例数が少なく困難が予想されるが、追跡期間を成人まで延長すれば、状況は異なる。心臓病や 2 型糖尿病等の慢性の非感染性疾患も同様に成人まで追跡することで調査可能となる。さらに、過去の詳細な曝露状況が把握可能であることから、母親と父親についても引き続き調査対象として追跡することを推奨する。

本調査は、予算が非常に限られているにもかかわらず、大きな成果を出すことが求められている。長期的な計画の立案には、事前の予算確保が不可欠であり、おそらく 5 年単位での予算確保が適切である。日本人がエコチル調査を広く認知し、調査の重要性を理解してもらうためにも、著名人を広告塔として置くと良いだろう。このような活動は、調査参加意欲の維持にも効果的である。

2 エコチル調査研究計画

2.1 全体調査と詳細調査の研究計画と進捗

エコチル調査の全体調査は、100,000 人の調査参加者から構成される。生体試料は、母親、子ども、父親から採取する。質問票調査は、妊娠中、出生時、出生後 1 か月、6 か月、及びその後 6 か月ごとに、子どもが 13 歳に達するまで行われる。また、医療記録、住民基本台帳、及び学校保健記録の写しも収集される。2019 年 7 月現在、103,095 人の母親、100,323 人の子ども、51,908 人の父親をリクルートし、95,595 人の子どもをフォローアップしている。健康アウトカムは質問票調査を通じて収集され、先天異常、精神神経発達、免疫系及び代謝/内分泌系に関する質問が含まれる。質問票は、曝露測定値（化学物質、屋内空気汚染物質、騒音、その他の汚染物質及びアレルゲン）及び共変量と交絡因子（親と子）に関する情報の収集にも使用される。血液及び尿は、母親（妊娠初期、妊娠中期～後期、出産時）及び父親（随意）から採取した。母親からは、母乳（1 か月）及び毛髪（出産時）を、子どもからは、臍帯血、ろ紙血（1 か月）及び毛髪（1 か月）をそれぞれ採取した。妊娠中期～後期の母体血は金属元素（Hg、Pb、Cd、Mn、Se）とペルフルオロアルキル物質（PFAS）を、妊娠前期の母体尿はコチニン、8-OHdG、有機リン系農薬代謝物（DAP)、環境フェノール（パラベン、ビスフェノール、トリクロサン等）をそれぞれ分析した。現在、妊娠中期～後期の母体尿のフタル酸エステル及びネオニコチノイド系農薬の分析を行っている。

詳細調査は、全体調査の全参加者から無作為に抽出された 5,000 人の参加者で構成される。詳細調査では、1.5 歳及び 3 歳時に、屋内及び屋外の空気汚染物質、粒子状物質、ハウスダスト、騒音、住宅環境調査のための家庭訪問が行われる。2、4、6、8、10 及び 12 歳時には、心理発達検査、身体検査、血液及び尿の採取を行う。発達検査は、2 及び 4 歳時には新版 K 式発達検査（Kyoto Scale of Psychological Development）を、8 歳時には computer assisted testing（CAT）を利用した検査を実施した。身体測定、血液検査、皮膚の視覚的な検査を含む医学的検査は、2、4、6、8、10 及び 12 歳時に行われる。8 歳時には、呼気 NO 及び呼吸機能検査も実施する。採取した血液試料は、化学物質及び抗体（非特異的 IgE、特異的 IgE、IgA、IgG1 及び IgG4、麻疹抗体)、甲状腺ホルモン（TSH、FT4、T4、T3、fT3)、25（OH）ビタミン D、IGF-1、LH、FSH、ステロイドホルモン、HbA1c、グルコース、インスリン、LDL、HDL や TG を含む健康

バイオマーカーについて調査される。

学童期検査は、コホート全体、つまり参加者 100,000 人を対象として実施する予定である。小学 2 年生の検査（8 歳）は 2019 年 7 月に開始し、身体検査、computer assisted testing（CAT）を利用した発達検査及び尿採取を行っている。

曝露評価のツールには、バイオモニタリング（血液、尿、母乳、毛髪）、環境測定、質問票、モデリングが含まれる。様々な化学物質及び生化学マーカーが、その物質に応じて、全試料（全体調査）またはより小規模な試料（詳細調査及びコホート内症例対照研究）で分析予定である。血液（金属（Cd、Hg、Pb、Mn、Se）、PFAS、Me-Hg）及び尿（コチニン、8OHdG、フェノール（パラベン、ビスフェノール等）、有機リン代謝物）の分析手法開発が完了し、母体血、母体尿、臍帯血試料の分析に適用された。血中残留性有機汚染物質（POPs）及びダイオキシン類（芳香族炭化水素受容体活性化合物）の分析、尿中のピレスロイド代謝物及びヒ素化合物の化学形態別分析の手法は現在開発中であり、尿中のフタル酸及びネオニコチノイド検出の手法開発は完了間近である。現在、ウェアラブルセンサーとサンプラーの活用や歯の分析を検討中である。環境測定は、詳細調査で行われる。曝露評価を目的とした標準的な質問票は存在しないため、エコチル調査独自の質問票の開発を試みている。モデリングに関しては、逆距離重み付け補間、土地利用回帰モデル、衛星画像/データ、人工的に作られた都市等の環境（built environment）、緑度、薬物動態モデリング等、様々なアプローチについて検討が行われている。

2.2 討論

分科会では、以下の討論が行われた。

- 調査対象物質と試料分析
  - 本調査の目的を完遂するには、戦略的なアプローチが必要である。
  - すべての対象化学物質をコホート全体で分析する必要はない。たとえば、従来の POPs の数を減らすことも一案である。今後も新規懸念物質が増え続けることからも、過剰な分析試料数は調査を停滞させる。
  - 最適なサンプルサイズの検討が必要である。必要なサンプルサイズは、調査目的（日本の地域間の違い等）によって異なる。長期的な傾向の把握には、出生コホートの繰り返し測定ではなく、横断研究の繰り返しが必要である。

- PFAS を 28 種類測定するエコチル調査の取り組みは良いが、PFAS には 500 を超える関連物質が存在し、すべてを測定する方法はない。さらに、我々が考えもしなかった種類の化学物質に曝露されていることもある。untarget 分析の導入は、一つの進め方かもしれない。
- 既に影響が知られている化学物質の影響を本調査において再度確認することは、研究の妥当性を証明し、調査の資金提供源及び政策立案者に研究の重要性を示す上でも役立つ。同時に、未知の化学物質の影響を調査することも重要である。生体試料の量には限りがある。Ko-CHENS は、少量の試料から様々な物質を同時に分析する手法の開発に取り組んでいる。しかし、すべての化学物質は分析できないため、非標的型スクリーニング分析を用いる必要がある。
- エコチル調査内に「探索コホート」を設置し、コホートの一部で untarget 分析を実施し、その結果をもとに重要化学物質の優先度を検討する方法もある。エコチル調査は、untarget 分析に適した手法の開発に取り組んでいる。
- 最初の曝露評価結果を活用し、新しいサブコホートを追加することも一案である。例えば、水銀の閾値検討を目的とした、水銀のサブコホート調査の実施である。血液試料中の水銀について、魚の消費に関する自己回答情報と合わせた調査も可能である。幅広い曝露をカバーするよう慎重に設計したサブコホート調査は、そのような研究課題や社会的ニーズにも応え、新たな仮説設定のきっかけを生むだろう。
- コホート内症例対照研究を実施し、仮説の検証に、エコチル調査のより大きなサンプルサイズを活用することも一案である。
- 他の研究所や研究機関と協力することで、エコチル調査の作業負荷を軽減し、調査の生産性の向上が可能である。例えば、一部化学物質については、既に他の研究所で分析手法が確立されており、ルーチン分析が可能な場合もある。
- エコチル調査は、化学市場の動向を追跡し、市場における化学物質の使用状況の変化を確認する必要がある。エコチル調査は化学物質の規制効果を追跡することが可能であり、そのような情報は行政にとって重要である。例えば、ドイツは DINCH をモニタリングしている。エコチル調査は、2011 年から 2014 年に収集した試料と二年前に実施したパイロット調査で DINCH

を分析したが、DINCH は検出されなかった。
  - エコチル調査は、現在、分析の自動化により分析に必要な試料量と人による試料の取り扱い作業を削減しようとしている。エコチル調査では、外注契約した研究所が試料の化学物質分析を行っている。
  - エコチル調査には、分析必要試料量の最少化を含む最先端のバイオモニタリングプログラムの技術が含まれている。
  - エコチル調査は、代替難燃剤等の新しい化学物質を対象化学物質に追加してもよい。
  - 非残留性化学物質の調査は、通常一つか二つの時点でのみ行われる。エコチル調査は、critical window を見つけるために、三時点以上でそのような研究を行うことができる。
- バイオバンク
  - 生体試料分析を含む環境曝露の測定方法は、年々進歩しており、新しい方法が提案されている。研究を促進する上で、より柔軟な組織を構築することが望ましい。
  - 長期保存生体試料の利用には、より慎重なアプローチが必要である。自動化したバイオバンクや研究施設を含む、新しい独立した施設が必要である。
  - 確固としたバイオバンクの整備は、出生コホート研究における最も重要な要素の一つである。
- 尿試料はあくまでも一時点の試料であることから、その解釈には注意が必要である。例えば、調査対象としている曝露が食物に由来する場合、その濃度は食物摂取後にのみ高くなる。様々な研究の様々な尿測定値の間には多くのばらつきがある。その一方、尿試料の採取は、現場で実施可能な手法でなければならない。エコチル調査は大きなサンプルサイズを要するため、エコチル調査の尿の測定値は、日本の一般人口を十分に表すことができるだろう。
- エコチル調査は、これまでで最大数の母乳試料を有する。母乳を対象とした研究は他にもあるが、それらは 20 年前のものであり、そのサンプルサイズはエコチル調査よりも小さい。エコチル調査では、母乳試料を分析し、薬物動態モデリングによる子どもの母乳由来化学物質の血中濃度予測や評価方法の検討を行っている。
- 個人モニタリング

  - 米国では、カラフルなリストバンドの形をした個人サンプラーを子どもに配布したところ、より正確と思われる曝露の測定が実施できた。ハウスダストは、特に人々の屋内滞在時間の長さを考慮すると、人々が受けている曝露に関する情報を豊富に含む試料である。
  - 育児に関する質問を質問票に含めることで、子どもがどのように過ごしているか、例えば、子どもが保育所に行くかどうか等を知ることができ、曝露状況のより良い理解につなげることができる。
- エピジェネティクス解析、遺伝学、メタボロミクス解析
  - すべての完全なトリオ（母、父、子ども）の全遺伝子のゲノムワイド関連解析の実施を勧める。遺伝子データを有することで、国際研究への参加機会を増やすことができる。
  - エコチル調査はエピジェネティクス解析を行うべきある。
  - エコチル調査が参加者から同意を取得した時点では、遺伝子分析の詳細は決まっていなかった。エコチル調査は現在、遺伝子分析を計画しており、同意の再取得が必要な場合に必要となる参加者への通知方法について検討している。
  - 子どもの微生物叢の調査とともに、子どもがどのような栄養を摂取しているのか調査すべきである。微生物叢が人の健康に重要な影響を及ぼすことが明らかになりつつある。このような調査は、8、10、12 歳での実施を検討すべきである。
  - エコチル調査は、小さなサンプル集団を対象としたメタボロミクス調査の実施とその結果の活用を真剣に検討すべきである。メタボロミクスで反応のあったバイオマーカーを探索することは、研究を進める一方法かもしれない。
- 思春期調査
  - 思春期、特に思春期の進行の調査は非常に価値がある。IAB/JECS は、エコチル調査が追跡期間を延長し、一生涯を対象とすることを推奨する。
  - エコチル調査では、思春期評価の手法について現在検討中である。現時点の案は、質問票を用いた調査であり、これは倫理的な問題から思春期評価を医学的検査に含めることが難しいためである。
  - 臨床的な評価には価値がある。自己申告は、思春期の開始と終了の評価に

は用いることができるが、思春期の進行の評価には用いることができない。肥満と身体活動も思春期に影響を与えるため、同時に考慮する必要がある。
  - タナースケールの活用も一つの方法である。しかし、タナースケールの活用にあたっては、文化的な問題が存在する可能性があるため、社会科学者との協力が望ましい場合がある。例えば、ドイツでは、50% の子どもが体毛を剃っていたため、タナースケールを使用できなかった。
- 両親の健康
  - エコチル調査では、現在、母親または父親から追加的に生体試料を採取する計画はない。子どもの健康だけでなく、両親の健康状態にも目を向けるべきである。
  - 詳細調査における父親を対象とした精子等のエピジェネティクス調査は、興味深い研究テーマとなる可能性がある。母親に関しては、閉経との関連の調査の実施も一案である。
- 病因と健康アウトカムの優先度
  - このような曝露調査を行う理由は主に二つある。一つは曝露状況の把握であり、もう一つは病因の解明である。曝露の測定に価値はあるが、社会の関心は、子どもの学習能力や免疫状態への影響等にある。
  - エコチル調査は病因評価ができる可能性がある。エコチル調査は、健康アウトカムの優先度を上げ、その研究内容をより明確化する必要がある。
  - エコチル調査は、病気とのつながりを分析し、そのような健康リスクを防ぐ上での鍵となるアプローチを伝えることで、社会に貢献できる。
- エコチル調査の研究実施体制
  - エコチル調査の運営委員会及び委員会に、医学または毒性学の専門委員会は設置されていない。見るべきアウトカムが多くあることから、アウトカムをテーマとした委員会が必要になるかもしれない。
  - エコチル調査は、研究実施体制について実用的である必要がある。ノルウェーの MoBa（Norwegian Mother, Father and Child Cohort Study）では、特定のトピックに関するアドホック会議の適宜開催が役立った。
- エコチル調査は、福島県に大規模なコホートを有している。エコチル調査は現在、地震の影響を特別に解析する予定はないが、そのような研究の実施が推奨される。

- その他研究で考慮すべき事項
  - エコチル調査は、免疫システムへの影響をより詳細に調べる必要がある。自己免疫疾患と関節リウマチを調査対象に追加してはどうか。
  - エコチル調査は、聴力検査の実施を検討すべきである。聴力検査は比較的簡単に実施できる上、化学物質の曝露が聴力低下に関連しているとの報告もある。
  - 青年期によく見られるメンタルヘルス、うつ病、不安について、ソーシャルメディアの役割とともに調査してはどうか。
  - エコチル調査は、飲料水からの曝露分析を検討すべきである。対象としている化学物質の多くは飲料水にも含まれている。試料は、8 歳の家庭訪問時に採取可能である。
  - エコチル調査は、可能な限り食事摂取量を評価すべきである。食事の写真は、食事の追跡に役立つ。
  - エコチル調査は、水、歯磨き粉、うがい薬等から曝露される可能性のあるフッ化物への曝露状況を把握するため、尿中フッ化物の分析を検討すべきである。
- IAB/JECS は、エコチル調査が上記のすべてを単独で実施できるとは考えていない。これらの提案は、他の研究グループとの協力により、達成できるかもしれない。
- エコチル調査は、調査の焦点や目的をより明確に示した戦略文書を作成する必要がある。

2.3 助言

IAB/JECS は、エコチル調査が、より新しい曝露評価手法を研究に組み込むことを勧める。例としては、シリコン製リストバンドを使用した統合的な個人曝露評価、スマートフォンを使用した活動記録や食事写真の撮影、乳歯を用いた後ろ向きの曝露評価や高感受性期間（windows of susceptibility）の評価等である。

尿に関しては、尿サンプルがいつ/どのように採取されているか不明である。体内半減期が短い汚染物質の場合、特に重要な感度のタイミング（timing of critical sensitivity）がまだ不明な場合は、試料を複数回採取する必要がある。ハウスダストについては、カ

ビやアレルゲンのみならず、更に他の項目についても調査すべきである。ハウスダスト、または子どもが長時間滞在する保育所や学校のダストは、化学物質への主な曝露源である。さらに、水道水中に含まれる物質は埃や空気中の物質と同等に重要であることから、家庭訪問時には水道水の採取も行うべきである。

エコチル調査は、レガシー化学物質ではなく、特に 10 年前には気にも留めていなかった新規物質を分析対象に加える検討をすべきである。追加対象物質の例としては、有機リン系難燃剤の代謝物、塩素化パラフィン、代替臭素化難燃剤、多くの PFAS 等がある。尿中フッ化物は測定すべきである。しかし、すべての対象物質をすべてのサンプルで測定する必要はない。エコチル調査は、研究課題と測定対象との間の関連に焦点を当てた新しいサブコホートの設置を検討すべきである。

現実世界において我々は複雑な混合物に複合的に曝露されている。untarget 分析の実施や、エクスポソミクス、メタボロミクス、プロテオミクス、リピドミクス分析等のオミクス解析の検討は非常に重要である。

エコチル調査は、免疫システムへの影響をより詳細に調査すべきである。例えば、感染症の発生率やジフテリアと破傷風の予防接種の成功である。北海道スタディで用いたアプローチとに他手法の活用も可能である。1 型糖尿病及びその他の自己免疫疾患の発生率も調査すべきである。主要なサイトカインの測定も必要である。血中のコルチコステロイドレベルをストレスの簡易な尺度として測定することも可能である。コルチコステロイドの測定は母親を対象とするには遅すぎるかもしれないが、子どものサブコホートで行うことができるだろう。

エコチル調査が追加を検討すべきその他健康アウトカムは、子どもの聴力、腎機能、肝機能、及び思春期の開始、期間、終了である。肝機能の評価については、エコチル調査が計画している指標よりも感度の高い指標がある。壊死とアポトーシスを区別できるサイトケラチン 18 を検討すべきである。思春期に関しては、男女ともにタナースケールの使用を検討すべきである。エピゲノムは、研究の複数の時点で調査すべきである。糞便微生物叢試料は、8 歳時と思春期に達した後も子どもから採取すべきである。この調査により、食事が環境曝露の影響を調整するだけでなく、食事自体の明確な影響を示すことが可能となる。

福島県のコホートは、放射線と洪水の影響だけでなく、災害が集団に与える長期的な影響を調査する貴重な機会を提供する。特にメンタルヘルスの問題にも焦点を当てるべきである。

3 国際連携及び国際ハーモナイゼーション

3.1 討論

国際連携及び国際ハーモナイゼーションに関して、以下の討論が行われた。

- 他の研究所で既に開発されている分析手法もある。他の研究所、特にこのような分析をルーチンで行っている研究所との連携により、エコチル調査の作業負荷を軽減できる。このような連携は、他の財源からの追加の資金調達につながる可能性もある。
- ヒトバイオモニタリングの経験を有するドイツやカナダ、HBM4EU 等のネットワークとのパートナーシップは、エコチル調査に役立つだろう。
- Unterget 分析は、国際連携の良い機会である。
- カロリンスカ研究所等の外部研究者とエコチル調査との共同研究は、現在分析手法開発に重点を置いている。
- エコチル調査は、技術的及び手続き上の制限のために、生体試料を外部研究者と共有できない。試料準備にはロボットシステムの調達が必要である。また、エコチル調査では、国内の共同研究であっても、試料及びデータ共有のための枠組みが整っていない。試料及びデータの共有方法について現在検討中である。さらに、改正された個人情報保護法を遵守する必要がある。
- 科学界では透明性が重視されている。試料とデータ利用の制限は、共同研究の機会を制限する可能性がある。
- 特に遺伝学の結果を発表するには、国際協力が不可欠である。
- 小児がんについては、どのコホートも単独では成果を出せない。MoBa、デンマークの DNBC（Danish National Birth Cohort）とエコチル調査が協力しあうことは可能である。妊娠中の食事と小児がんは、MoBa、DNBC とエコチル調査の共同研究のテーマとなり得る。
- 品質保証及び品質管理システムが推奨される。
- ハーモナイゼーションは必ずしも必要ではない。
- データや試料を移動させずに共同研究を行う方法はある。欧州では、DataSHIELD がプラットフォームとして使用されている。MoBa 及び DNBC では、データへ

のリモートアクセスを提供しており、すべての解析をセキュリティが保護されたサーバー上で実施できる。

- エコチル調査は、国際協力資金を得るために、多国間協定に取り組むよう努めるべきである。
- 外部申請者は複数の主任研究者を活用するを活用する方法もある。
- 論文投稿手順
  - エコチル調査では、論文投稿前の内部承認手続きに 6 週間が必要である。この手順は、論文の品質確保と論文の重複を避けるために設定された。
  - MoBa は、論文投稿に関する手続きを減らした。例えば、MoBa では当初、博士課程の学生の投稿の優先権を与えていたがその制度は廃止された。また、論文の科学的品質についても、個々の科学雑誌によって審査されるため、MoBa 内で独自の審査は行わないこととした。
  - エコチル調査は、将来の共同研究のために、データ分析と論文投稿に必要な手順をウェブサイト上で図示すべきである。
- エコチル調査は、できる限りその結果を英語の国際誌で発表すべきである。
- エコチル調査は、国際協力と分析手法のハーモナイゼーションに多大な努力を払ってきた。将来的には、新しいバイオマーカーを使用した分析方法に関して、新しい研究協力が必要である。

3.2 助言

エコチル調査は、世界的な評価と賞賛を得ている。国外の科学者がエコチル調査の科学者と協力する機会は複数あるべきであり、エコチル調査が提供するプラットフォーム上で彼ら自身の研究課題についての研究が可能となるべきである。エコチル調査の試料とデータは、無論厳重に管理された方法で、可能な限り早く他の研究者が利用可能とする必要がある。研究結果は、可能な限り迅速に、査読付きの国際誌で公表すべきである。

エコチル調査は、世界の四大出生コホート調査の一つであり、調査手法のハーモナイゼーションは必要に応じ試みるべきであろう。もちろん、エコチル調査は MoBa や DNBC よりも新しい調査である。

フランス、ドイツ、ノルウェー、デンマーク、中国、米国及び日本を含む国際出生コ

ホートグループへの参加は称賛される。

4 将来の計画

4.1 今後の調査研究計画

10 歳、11 歳、12 歳の子どもを対象とした自己記入式質問票による調査が計画されている。調査内容を説明するパンフレットが質問票とともに郵送される予定である。発達検査（Continuous Performance Test、Mental Number Line、Dimensional Change Card Sorting Test、Finger Tapping Test）は 8 歳と 12 歳での実施が計画されており、WISC-IV 知能検査は 10 歳での実施を検討中である。身体測定、血液検査、視覚検査は 2、4、6、8、10 及び 12 歳で継続実施予定である。10 歳以降の血液検査のバイオモニタリング項目は現在検討中である。呼気 NO 及び呼吸機能検査の実施が 8 歳で計画されており、思春期及び微生物叢の検査については検討中である。6 年生の検査は 2023～2026 年に予定されており、身体検査、発達検査、血液及び尿の採取が含まれる。

4.2 討論

分科会では、以下の討論が行われた。

- 13 歳で調査を打ち切り、生涯を対象としないことを支持する科学的な根拠はない。参加者を三世代にわたりフォローアップすることが理想的である。親をフォローアップしないことも貴重な機会を逸することになる。
- 青年期における化学物質の影響調査は非常に重要である。エコチル調査は、将来世代への影響を考え、調査期間を思春期まで延長すべきである。日本のバイオモニタリング事業は、成人のみを対象としており、小規模であるため、エコチル調査は出産適齢期の女性、胎児、乳児、子どものバイオモニタリングに関して重要な役割を担っている。エコチル調査のデータは、有害化学物質管理政策の確立に貢献することが期待される。エコチル調査が青年期以降にも延長されれば、有害物質への曝露と次世代への健康影響の把握に非常に重要な役割を果たし、低出生率や高齢化等の日本の社会問題への理解にも貢献するであろう。
- 認知機能試験にコンピューターゲームを活用してはどうか。
- 子ども向けの短いスマートフォン質問票を活用してはどうか。DNBC では、子

どもの年齢が上がるとともに質問票が短くなっている。子どもたちに食事摂取に関する質問を回答させることも考えられる。

- 思春期、青年期、及び若年成人期に起きていることを理解するには、行動科学の知識が必要である。
- 参加者とのコミュニケーション
  - 参加者を増やし、協力取りやめを最小限に抑えるためには、子どもや家族との接触を最適化することが重要である。子どもたちの間で人気のあるコミュニケーションメディアの活用は効果的である。エコチル調査には、そのようなツール開発に携わる社会科学者が必要である。
  - 10 歳以降、子どもたち自身がコミュニケーションのための資料開発に関与する方法もある。
- 参加者への結果返却
  - エコチル調査では、測定結果の数値と短い解説を調査結果として参加者に報告している。日本にはドイツの HBM 値に相当する指標はないため、提供できるデータ解釈は限られる。
  - ドイツとヨーロッパでは、自分の曝露レベルの把握が、調査への参加動機の一つとして挙げられている。エコチル調査では、参加者から結果返却に対して、肯定的及び否定的な反応のいずれもまだない。
  - 参加者が辞退しない限り、参加者にはすべてのデータを返却すべきである。米国では、コホート全体の値を参加者の個々の値と合わせて図示しており、参加者はコホート内おける自分の相対的な曝露レベルを確認することができる。
  - 異常値への対応について、エコチル調査では甲状腺ホルモンとビタミン D の基準がある。遺伝子関連の基準は現在検討中である。エコチル調査では、化学物質に関する指針値はないため、ケースバイケースで対応している。例えば、セレン濃度が高い参加者に連絡し、高曝露となった原因を突き止めた。
- コホートの維持管理
  - コホートの維持管理は重要であり、このユニークな調査の参加者であるという参加者のアイデンティティを高めることが重要である。特に 13 歳以降の調査継続を希望するのであれば、エコチル調査は、子どもとのコミュニ

ケーションの検討について、優先度を高めるべきである。
  - 米国は、全国的な子どもの調査を設立することができず、現在、多数のコホートの協力を得た合成コホート（ECHO プログラム）を設立しようとしている。米国は、ECHO プログラムを通じて、コミュニケーションが不可欠であることを学んだ。人々をつなぎ、参加者がプログラムに興味を持ち続けてもらうために、参加者である子どもたち同士が一緒に遊ぶ機会を設けた。参加者の関心を高め、参加者が自身のデータへの所有者認識を形成することが重要である。
  - ソーシャルメディアの活用は一つの方法である。例えば、DNBC は、Facebook や有名なユーチューバーを活用し、子どもたちに質問票への回答を促した。DNBC では、何人かの子どもたちを調査の代表大使として動画に登場してもらい、他の参加者へ参加を呼び掛けてもらった。
- アウトリーチ活動
  - エコチル調査の継続には、一般市民へのアウトリーチ活動が重要である。
  - カナダでは、アウトリーチ資料として調査概要を作成することが一般的である。エコチル調査では、環境省が毎年シンポジウムを開催し、エコチル調査の進捗を一般市民に周知している。さらに、各研究論文が科学雑誌に受理された場合、著者は環境省に受理を報告する際に日本語の抄録を提出する必要がある。著者は平易な言葉遣いを用いることが推奨されており、その日本語の抄録はウェブ上で公開される。さらに、論文が受理された際には、ユニットセンターでプレスリリースが行われる。
  - 他の科学者への周知を目的とした統合報告書の公表が推奨される。
  - 社会全体の化学物質曝露を減らすため、エコチル調査の結果は、利害関係者（ステークホルダー）と共有されなければならない。
  - エコチル調査は、環境省が調査の重要性を社会に対しより効果的に伝えられるよう、その目的で環境省が使用できる資料を提供する必要がある。
  - 現在エコチル調査は、社会科学者を雇用していない。参加者とのコミュニケーションはユニットセンターが担当し、コミュニケーションに活用可能な映像や資料の作成をコアセンターが担っている。エコチル調査は SNS アカウントを所有していない。
- エコチル調査には、調査結果の翻訳や政策への提言、コミュニケーションを担

当する社会科学者が必要である。

4.3 助言

全体的なコメントと勧告で既に述べたように、エコチル調査を 13 歳以降も継続すべき科学的理由は十分に存在する。子どもたちが成人し、可能であれば三世代までフォローアップできなければ、この調査に期待される成果の多くは失われるだろう。詳細調査の活用だけでなく、コホート内症例対照研究の実施が重要である。

膨大な試料数及びデータ数を完全に評価し活用するには、バイオバンクと環境試料バンクのアップグレードが必要である。ロボットシステムの調達は、高度なデータ管理システムのために不可欠である。

このコホートの継続にはコミュニケーション手段の強化が必要であり、例えばソーシャルメディアの更なる活用や調査参加者本人が調査に対する当事者意識を形成するための調査参加者による活動グループの形成等が手段として挙げられる。IAB/JECS は、社会科学者の雇用を強く推奨する。

対象の子どもが大人へと成長する過程を追跡するためには、対象者自身からインフォームドコンセントを得る適切な年齢を検討すべきである。

参加者がデータの取得を明示的に拒否しない限り、すべてのデータを参加者に返却する必要がある。また、国家的な参照値が存在しなかったとしても、参加者の個々の測定結果がコホート全体に対しどの位置にあるのかを示すことは可能である。

エコチル調査の可能性を最大限に引き出すには、人員の増強が必要である。IAB/JECS は、コアセンターの人員を約 2 倍に増員することを推奨する。

Japan Environment and Children's Study

International Advisory Board

Programme

September 2019

National Institute for Environmental Studies

1. International Advisory Board

1.1. Background

Japan Environment and Children's Study (JECS) is a nation-wide birth cohort study that involves over 100,000 mother-child dyads started in 2011. The National Institute for Environmental Studies (NIES) host JECS Programme Office that leads JECS in cooperation with the National Centre for Child Health and Development and 15 Regional Centres consisting of universities and medical institutions.

JECS entered the ninth year in 2019 with its children aging 4 to 7 years. All participant check-up is planned in 2019 at the age of 8. At this stage, we are planning the next phase of JECS. It is considered important to have advices from international experts on JECS future plan.

1.2. Anticipated advices

The International Advisory Board will focus on the following topics:

1) Advice on study protocols
   Scientific, public policy and ethical advices on the current JECS protocols are requested.
2) International collaboration and harmonisation
   Suggestions on international collaboration and harmonisation of methodologies are sought.
3) Next JECS
   Recommendations on the JECS beyond 13 years (next JECS) will be discussed.

1.3. Date and venue

Date: 2–3 September 2019

Venue: Ohyama Memorial Hall, National Institute for Environmental Studies

1.4. Member

Role	Name	Affiliation (Country)	Expertise
Chair	Linda Birnbaum	NIEHS (US)	Environmental health, toxicology
	Åke Bergman	Swetox (Sweden)	Environmental chemistry
	Ghislaine Bouvier	U Bordeaux (France)	Epidemiology, Elfe researcher
	Marike Kolossa-Gehring	UBA (Germany)	Toxicology, biomonitoring
	Per Magnus	NIPH (Norway)	Epidemiology, MoBa PI
	Sjurdur F. Olsen	SSI (Denmark)	Epidemiology, Deputy PI of DNBC
	Michael Borghese	Health Canada (Canada)	Epidemiology, MIREC study
	Kim Suejin	NIER (South Korea)	KoCHENS PI
	Leonardo Trasande	NYU (US)	Paediatrician, public policy

1.5. Attendees

JECS researchers are invited along with NIES researchers and Ministry of the Environment officials as an observer.

1.6. Report

Chair will compose a report document in cooperation with the IAB members. The report document will be published in accordance with the NIES IAB procedure.

2. International Advisory Board Meeting Agenda

1 September		IAB members arrive Tsukuba
2 September		Day one
	8:45	Arrival at NIES
	9:00	Opening remark (President)
	9:10	Introduction of IAB members, housekeeping announcement
	9:20	JECS overview
	10:20	Break
	10:30	Study overview (Main study, Sub-cohort study and school age examination)
	11:30	Lunch
	13:00	NIES campus tour
	14:15	Break
	14:30	Presentations from IAB board members (15 min x 9 members)
	17:00	Adjourn
	18:00	Reception
3 September		Day two
	9:00	Exposure assessment protocol and progress
	9:45	Future plan
	10:30	Break
	10:45	Discussion
	11:45	Lunch
	13:00	IAB member discussion, report drafting
	14:30	Break
	14:45	Comments and recommendations from IAB
	15:45	Closing remark (Vice president)
	16:00	Close of the meeting
4 September		Departure from Tsukuba

Japan Environment and Children's Study

International Advisory Board

Fact Sheet

September 2019

Japan Environment and Children's Study

1. Executive summary

Japan Environment and Children's Study (JECS) started in 2011 as a national birth cohort study that examines environmental impacts on children's health and development. The goal of JECS is to identify environmental factors that affect children's health in order to facilitate better environmental risk management. Specifically, the JECS focuses on the effect of exposure to chemical substances during foetal period and/or in early childhood. JECS gives priority to five major health domains: Reproduction and pregnancy complications; congenital anomalies; neuropsychiatric/developmental disorders; allergy and immune system disorders; and metabolic and endocrine system dysfunctions. In JECS, the environment is defined broadly such as global/ambient environment including chemical substances and physical conditions, built environment, behaviours/habits, socio-economic factors, family/community support and genetic factors. JECS recruits and collects outcome and exposure data/biological specimens from expecting mothers and then periodically follows their children until they reach 13 years of age as a main part of the study (Main Study). Additionally, a Sub-Cohort Study, involving 5,000 children randomly selected from the Main Study, is also designed to investigate the environmental factors and outcome variables more thoroughly, including home visits, ambient air measurements, psycho-developmental tests and paediatricians' examination.

The JECS is operated in cooperation among several research institutions. The Programme Office, or National Centre for JECS, which is situated in the National Institute for Environmental Studies (NIES), takes a directive role for the JECS, such as preparing standard operating procedures (SOPs) and storing collected data and biospecimens. The Medical Support Centre, which is organised within the National Centre for Child Health and Development, supports the Programme Office providing medical expertise. The Programme Office and Medical Support Centre cooperate together with 15 Regional Centres that are located in universities and other research institutions throughout Japan. The Regional Centres select study areas involving a single or multiple administrative district(s), taking account of their number of births, regional representativeness and level of potential exposure to chemical substances. The Regional Centres are responsible for recruiting and maintaining study participants and gathering data in their selected study areas at each study phase.

The participants of the Main Study are 100,000 pregnant women, their children and the children's fathers (when accessible). The participants of the Sub-Cohort Study are 5,000 children who are randomly extracted from those of the Main Study. The exposure assessment is conducted through chemical analyses of biospecimens collected from the participants (pregnant women, their children and the children's fathers), questionnaires, environmental monitoring and modelling/computer simulations. The biospecimens include blood, urine, umbilical cord blood, breast milk and hair. The health outcomes are measured primarily through questionnaires and medical record transcriptions, while medical examination and clinical blood testing are also performed. For the Sub-Cohort Study, more extensive methods of measurement for both environmental factors and health outcomes are employed, such as ambient air monitoring, a neurodevelopmental test, paediatricians' examinations and blood tests.

By March 2014, participants (pregnant women) solicitation for the Main Study was completed. The registered mothers reached 103,106, resulting in 100,169 births. The number of fathers counted 51,943 (those numbers are being confirmed). For each participant, questionnaires are administered twice during pregnancy, at birth, a month after birth, 6 months old and every subsequent 6 months. The response rate for each questionnaire has been maintained over 70%–80%.

To date, 64 articles using JECS data have been published in peer-reviewed journals.

Attachment:

1. Japan Environment and Children's Study (JECS) Study Protocol
2. Japan Environment and Children's Study (JECS) Sub-Cohort Study Protocol

2. Study overview

2.1 History

Throughout the world, there has been a growing concern regarding the effects of environmental pollution and chemical contaminants in the environment on children's health and development. In 1997, the Miami Declaration on Children's Environmental Health was adopted at the G8 Environment Ministers' Meeting. In late 1990's, Denmark, Norway and the United States commenced large-scale birth cohort studies of the 100,000 size to investigate the effects of the environment. In 2009, the importance of children's environmental health was highlighted again at the G8 Environment Ministers' Meeting held in Syracuse, Italy, where ministers agreed to cooperate in scientific research to push this movement forward.

Along with such development, a great deal of research has been conducted to evaluate the impact of the environment on human health. However, as most of such studies were conducted with laboratory animals, their findings may not necessarily address possible effects occurring under the current exposure levels in humans. This led Japan to recognize the importance to conduct its own birth cohort research, which enables us to directly observe the effects of environmental factors on humans. (Report of the Conference on Epidemiological Study of Children's Environmental Health, March 2008).

In August 2006, the MOE held a conference focusing on children's vulnerability to environmental hazards. In April 2008, MOE organised the Expert Group on the Epidemiological Research for Children's Environmental Health (later converted to JECS Working Group) and started planning a nation-wide epidemiological study. After small-scale pilot studies were conducted at several locations in Japan to examine the appropriateness and feasibility of the study plan, in March 2010, the Working Group published a conceptual plan for a large-scale birth cohort study which defined JECS.

2.2 Study objectives

JECS is a nation-wide birth-cohort study that follows children before birth to age 13. The goal of the JECS is to identify environmental factors that affect children's health and development during the foetal period and/or in early childhood, in order to help the government formulates measures to safeguard the environment for future generations. To search environmental factors with potential impacts as broadly as possible, JECS created an extensive list of chemical compounds and evaluate their effects on children. The target compounds include metals/elements, chlorinated persistent organic pollutants (POPs), brominated POPs, pesticides, organofluorine compounds, aroma compounds, phthalate metabolites, phenols, and many other compounds (Table 1). The chemical compounds subject to analyses are selected from Table 1, taking into account the needs and importance for the examination of core hypotheses.

Table 1: JECS selected target compounds

Group	Target compounds
Metals/elements	Lead, cadmium, elemental mercury, methyl mercury, manganese, selenium, arsenic, organic arsenic compounds, iodine
Chlorinated POPs (persistent organic pollutants)	Polychlorinated biphenyls (PCBs), hydroxylated PCBs (OH-PCBs), dioxins and furans (PCDDs, PCDFs, co-PCBs), hexachlorobenzenes (HCBs), pentachlorobenzenes (PeCBs)
Brominated POPs	Polybromodiphenylethers (PBDEs), polybromobiphenyls (PBBs), hexabromocyclododecans (HBCDs)
Pesticides	Chlordanes, DDT and its metabolites (DDE, etc.), drins (dieldrin, etc.), heptachlor, hexachlorocyclohexanes (HCHs), mirex, chlordecone, toxaphene, organophophorus pesticide metabolites (DMP, DEP, DMTP, DETP, etc.), fenitrothion metabolite (methylnitrophenol), acephate metabolite (methamidophos), pyrethroid metabolites (PBA, DCCA, etc.), dithiocarbamate fungicide metabolites (ethylene thiourea, etc.), neonicotinoid metabolites, pentachlorophenol (PCP), atrazine, dymron, glyphosate, flutolanil, iprodione, flusulfamide
Organofluorine compounds	Perfluorinated alkyl acids (PFAAs), polyfluorinated telomer compounds
Aroma compounds	Nitromusks, cyclic musks
Phthalate metabolites	Mono (2-ethylhexyl) phthalates
Phenols	Bisphenol A, Nonyphenols, Parabens
Others	Triclosan, benzophenone, *N,N*-diethyl-meta-toluamide (DEET), polyaromatic hydrocarbons (PAHs) and their metabolites (1-hydroxypyrene, 3-hydroxyphenanthrene, etc.), cotinine, thiocyanate, dichlorobenzene, phytoestrogen, caffeine, pyridine, acrylamide, tributyl phosphate, tributoxyethyl phosphate, 8-hydroxydeoxyguanosine (8-OHdG)

The JECS priority health outcomes are reproduction and pregnancy complications, congenital anomalies, neuropsychiatric/developmental disorders, allergy and immune system disorders and metabolic/endocrine system dysfunctions (Table 2).

Table 2: Health Outcomes

Category	Items
Pregnancy/reproduction	Sex ratio, abnormal pregnancy, miscarriage, stillbirth, preterm delivery, birth weight, physical development after birth (e.g., motor function, kidney function, and lung function), etc.
Congenital anomalies	Hypospadias, cryptorchidism, cleft lip and palate, intestinal atresia, ventricular septal defect, chromosome aberration
Neuropsychiatric developmental disorders	Developmental delay or deviation (mental retardation and other cognitive difficulties), autism spectrum disorder, learning disorder (LD), attention deficit hyperactivity disorder (ADHD), mental disorders (e.g., gender identity disorder), and other symptoms and behavioural characteristics
Allergy and immune system disorders	Food allergy, atopic dermatitis, asthma, allergic rhinitis, Kawasaki disease, etc.
Metabolic and endocrine system disorders	Abnormal glucose tolerance, obesity, effects on reproductive organs, genital dysplasia, sex differentiation of the brain, etc.
Childhood tumours	Leukaemia, brain tumours, etc.

2.3 Study protocol

2.3.1 Study design

JECS is a longitudinal birth cohort study involving 100,000 mother–child dyads, and if accessible fathers. The Main Study includes all the participants. The information about pregnancy and children's health outcomes is collected by questionnaires and medical record transcriptions during pregnancy and after birth until children become 13 years of age. Besides the Main Study involving all the participants, 5,000 children are randomly selected from the Main Study and subject to more extensive measurements of both environmental factors and health outcomes, including ambient air monitoring, a neurodevelopmental test, paediatricians' examinations and blood tests.

2.3.2 Participants

In the Main Study, the participants are 100,000 pregnant women, their children and the children's fathers if accessible. The inclusion criteria are: 1) their expected delivery date is between 1 August 2011 and 31 March 2014 and 2) they live in one of the study areas selected by Regional Centres at the time of recruitment.

The participants are recruited by the Regional Centres through the following two methods. The first is to recruit through cooperating health care providers (CHCPs). Regional Centres request cooperation from all of the health care providers that pregnant women living in the study areas possibly visit for prenatal care and/or delivery. The pregnant women living in the study areas who visit the CHCPs are asked to participate in the study. The second recruitment method is to use local government offices such as public health departments. When pregnant women living in the study areas apply for the Mother and Child Health Handbook[1], or a pregnancy journal, at the local government offices, Regional Centres contact them and ask for their participation. When they show interest in the study, trained field staff, or Research Coordinators, from the Regional Centres acquire the information from the pregnant women about which health care providers they would visit for prenatal care and delivery. If the health care providers are designated as CHCPs, the pregnant women are then asked to participate in the study.

The participants of the Sub-Cohort Study are 5,000 children who are randomly selected from those of the Main Study. The Programme Office creates soliciting lists by extracting children randomly from those who are born during a certain period so that the age of the participants at the time of data collection falls within a limited

[1] An official booklet given complimentary to all expecting mothers in Japan when they get pregnant in order to receive municipal services for pregnancy, delivery and childcare.

range (e.g., 24–27 months). The total number of the children on each recruiting list is estimated based on the results of recruitment of participants for the Main Study. The number of the children extracted for the list who reside in the study area of each Regional Centre is designed to be proportional to the number of the participants of the Main Study in the area. The parents/legal guardians of the selected children are reached through phone-call and asked their consent of children's participation in the Sub-Cohort Study.

2.3.3 Instruments

Environmental factors

In JECS, the environment is defined broadly such as global/ambient environment including chemical substances and physical conditions, built environment, behaviours/habits, socio-economic factors, family/community and genetic factors. The exposure analyses are conducted through chemical analyses of biospecimens collected from the participants (pregnant women, their children and the children's fathers), questionnaires, environmental monitoring and modelling/computer simulations. The biospecimens include blood, urine, umbilical cord blood, breast milk and hair. The Programme Office develops analytical methods, procedures and models which are provided to contract laboratories that meet the required specifications including ISO/IEC 17025:2005 accreditation and the analysis specific quality assurance/quality control requirements. Resulting data are sent back to the Programme Office in the specified format (i.e. electronic data deliverable) and then stored in the central data management system (DMS) after the automated data review process.

Health outcomes

JECS' priority outcomes are reproduction and pregnancy complications; congenital anomalies; neuropsychiatric/developmental disorders; allergy and immune system disorders; and metabolic and endocrine system disorders. These outcomes are measured not only by diagnoses but also by symptoms and signs. Questionnaires and medical record transcriptions are the two major instruments for the outcome measurements. Paediatricians' and psychologists' examinations as well as clinical blood testing are also conducted at certain ages of the Sub-Cohort Study (ages of 2, 4, 6, 8, 10 and 12) For highly prioritized outcomes, the detailed information (i.e., phenotypes, clinical test results) are collected from the corresponding medical records. School age examination inviting all participating children will be conducted when they become second and sixth grades of elementary schools.

Covariates and potential confounders

JECS collects the information about outcome and exposure covariates and potential confounders. Such include demographic variables (e.g. address, education, employment, house-hold income), lifestyle/behaviour factors (e.g. stress level, diet, smoking and alcohol habits, exercise, sleep condition), physical environment (e.g., heat, ionising radiation, housing condition, and neighbourhood), social/psychological factors (e.g., personality, social/community support), medical history (including pregnancy history) and medical history of family members.

2.3.4 Milestones

The recruitment of participants starts in January 2011 and continues for three years. The participating children are followed until they reach the age of 13 years. The JECS is planned to continue until 2032, allowing five years for data analysis after all the data collection are completed.

During their pregnancy, the data of the enrolled mothers are collected twice, once in early pregnancy and once in the mid-to-late pregnancy through administering questionnaires, gathering biospecimens and referring their medical record during pregnancy. After the mothers give birth, questionnaires are sent to them every 6 months. The information in the Mother and Child Health Handbook is transcribed to gather additional data regarding the children's growth and development. Table 3 shows the milestones of the Main Study and Sub-Cohort Study. Study protocols for 6 years and later are under development.

Table 3: JECS milestones

Milestones	Instruments (Main Study)	Instruments (Sub Study)
At recruitment (first trimester)	Medical record, Questionnaire Biospecimen [Mother: blood (30 ml) and urine (50 ml), Father: blood (30 ml)]	
Second or third trimester	Questionnaire Biospecimen [Mother: blood (30 ml) and urine (50 ml)]	
At delivery	Medical record Biospecimen [Child: umbilical cord blood (20–35 ml)]	
Within a few days after birth (during hospitalization)	Biospecimen [Mother: blood (20 ml), hair (2 mg), Child: dried blood spot]	
1 month old	Medical record, Questionnaire Biospecimen [Mother: breast milk (20 ml); Child: hair (2 mg)]	
6 months old	Questionnaire	
1 year old	Questionnaire	
1.5 years old	Questionnaire	Environmental measurements
2 years old	Questionnaire	Developmental test Medical examination (blood test, skin examination, etc.)
2.5 years old	Questionnaire	
3 years old	Questionnaire Mother and Child Health Handbook transcription	Environmental measurements
3.5 years old	Questionnaire	
4 years old	Questionnaire	Developmental test Medical examination (blood test, skin examination, etc.)
4.5–5.5 years old	Questionnaire (once every 6 months)	
6 years old	Questionnaire	Developmental/Neuropsychological test and/or interviews (at 6, 8, 10 and 12 years old) Medical examination (blood test, height measurement, etc.; at 6, 8, 10 and 12 years old) Environmental measurements (once or twice, under consideration)
7–11 years old	Questionnaire (once every year) School age questionnaire (once every grade)	
8 years old	School age examination Physical measurements Developmental test (CAT) Urine collection	
12 years old	Questionnaire School age examination Physical measurements Developmental test (CAT) Blood tests Urine collection	

2.4 Organisation

JECS is conducted in cooperation among several different organizations: Programme Office, Medical Support

Centre and 15 Regional Centres.

The Programme Office, which is situated in the National Institute for Environmental Studies (NIES), is taking a leading role for JECS, including accumulating data collected by Regional Centres; maintaining the database, or data management system (DMS); maintaining the repository of biological and environmental specimens; and performing exposure measurements including chemical analyses on the specimen. The Programme Office prepares standard operating procedures (SOPs); carries out administrative tasks; provides administrative and technical support for Regional Centres and is responsible for risk management and public communication.

The Medical Support Centre is established in the National Centre for Child Health and Development. The Medical Support Centre develops outcome measurement instruments. The Medical Support Centre is also responsible for preparing SOPs, training personnel who are responsible for collecting data regarding to health outcome variables at each Regional Centres and providing Regional Centres with medical advices when necessary.

The Regional Centres are placed in universities and other research institutions in different locations of Japan. The Regional Centres are responsible for recruiting study participants and contacting them, such as explaining the study protocol, obtaining the written consent, registering the participants, collecting biospecimens, transcribing medical records, entering questionnaires into the DMS and field operation for the Sub-Cohort Study home visits.

The Steering Committee is the highest decision making body of JECS (Figure 1). Subcommittees are formed under the Steering Committee to discuss specific aspects of the study such as publication, communication/outreach, exposure analysis, pilot study conducts, epidemiological/statistical methodologies and ethics. In addition to these committees. Working groups are placed under the Programme Office and Medical Support Centre to draft study protocols and procedures, including developing questionnaires, planning the Sub-Cohort Study and selecting chemistry methods.

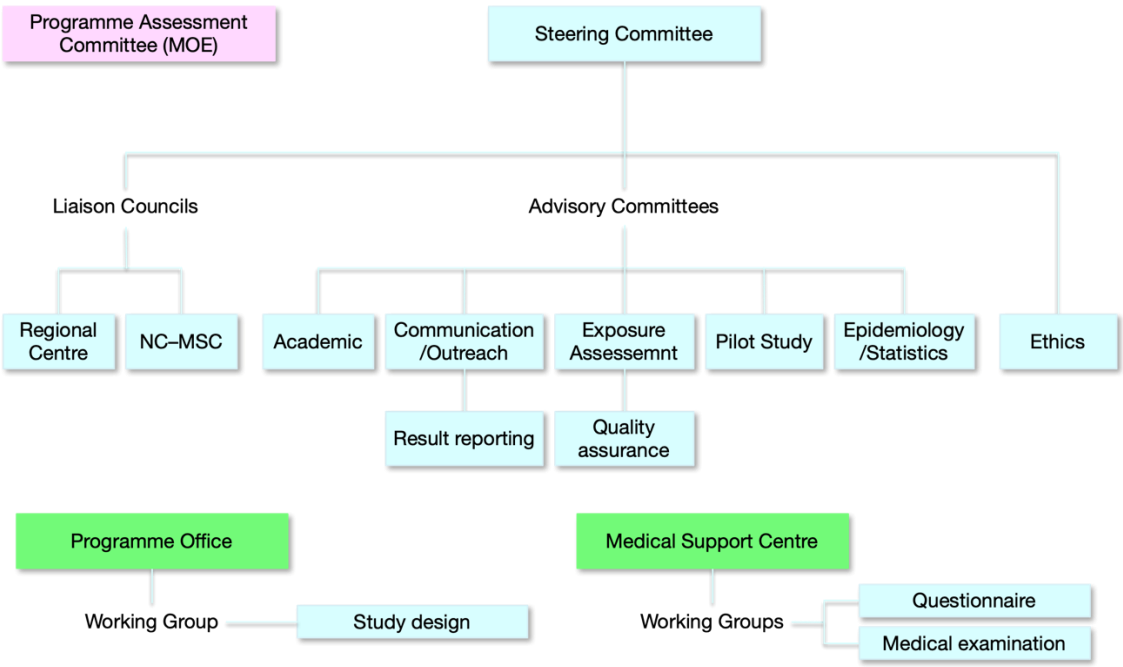


Figure 1: JECS Governing and committees

2.5 Funding

JECS is funded directly by the MOE under parliament approval. The annual budget is shown in Table 4.

Table 4: Annual funding for JECS

Fiscal year (April–March)	**Billion yen**[2]	**Million US dollar (rate = 1 USD/110 yen)**
2010	3.1	28
2011	4.6	42
2012	6.1	55
2013	6.1	55
2014	5.7	52
2015	5.7	52
2016	5.8	53
2017	5.8	53
2018	5.9	54
2019	5.9	54

2.6 International collaboration

The MOE organised a workshop in February 2011 in Tokyo and initiated a discussion about possible study harmonisation among some large-scale 21st century birth cohort studies. Investigators associated with major studies decided it was worthwhile to harmonise study protocols and procedures prior to, or in conjunction with, each study's progress in order to make future data pooling easier. A working group was formed to define a list of core elements for inclusion in the new birth cohort studies, such as health outcome measurements, biomarkers, exposure measurements, questionnaire harmonisation, data management and study process. France, Germany, Shanghai (China) and the United States that were planning or conducting new large-scale studies of environmental influences on children's health and development showed interest in participating in the group. In late 2011, experts from these five countries constituted the Environment and Child Health International Birth Cohort Group (ECHIBCG). The group meets periodically along with monthly telephone conferences to exchange information about each study protocol and process and to discuss possible measures of harmonisation. Recently the group also shared a common biological sample and performed a round-robin trial for lead and mercury analysis in order to identify potential quality assurance/quality control problems. JECS plays a key role in this group.

The sample size of JECS, 100,000, is not considered sufficient to evaluate the association between environmental exposures and childhood cancers. JECS collects the information about cancers in order to contribute to international pooled data analyses. JECS is a participant of the International Childhood Cancer Cohort Consortium (I4C).

3. Current status

3.1 Participation

Recruitment of participants (pregnant women) for the Main Study was completed in March 2014. The consent rate of mothers was approximately 80%. As of 31 August 2015, 103,086 mothers and 51,943 fathers are registered with 100,169 live births being recorded (Table 5, Figure 2). For each participant, questionnaires are

[2] Budget includes funding for the Programme Office, Medical Support Centre and Regional Centres.

administered during pregnancy, at birth, a month after birth, 6 months old and every subsequent 6 months. The eldest children have become 4 years old as of 1 October 2015.

Selection of the participants for the Sub-Cohort Study and their recruitment through phone call started in October 2014. By the end of March 2015, all the Regional Centres completed the selection of participants from the first wave (those born between April and June 2013) and the second wave (those born between July and September 2013). The Regional Centres started to contact participants selected from the third wave. Approximately 50% of the participants contacted have agreed for their children's participation.

Table 5: Number of participants as of July 2019

Regional Centre	**Recruitment**			**Follow-up**
	Mothers	**Children**	**Fathers**	**Children**
Hokkaido	8,362	7,932	2,890	7,491
Miyagi	9,217	8,999	4,161	8,550
Fukushima	13,131	12,866	8,693	12,270
Chiba	6,191	6,010	3,975	5,608
Kanagawa	6,652	6,404	2,444	5,947
Koshin	7,335	7,169	5,016	6,708
Toyama	5,584	5,389	3,279	5,160
Aichi	5,721	5,554	2,575	5,350
Kyoto	3,982	3,898	3,145	3,753
Osaka	8,043	7,851	3,004	7,657
Hyogo	5,187	5,069	1,897	4,843
Tottori	3,059	3,036	1,149	2,927
Kochi	7,094	6,920	2,386	6,603
Fukuoka	7,691	7,517	3,809	7,242
South Kyushu/Okinawa	5,846	5,709	3,485	5,486
	103,095	100,323	51,908	95,595

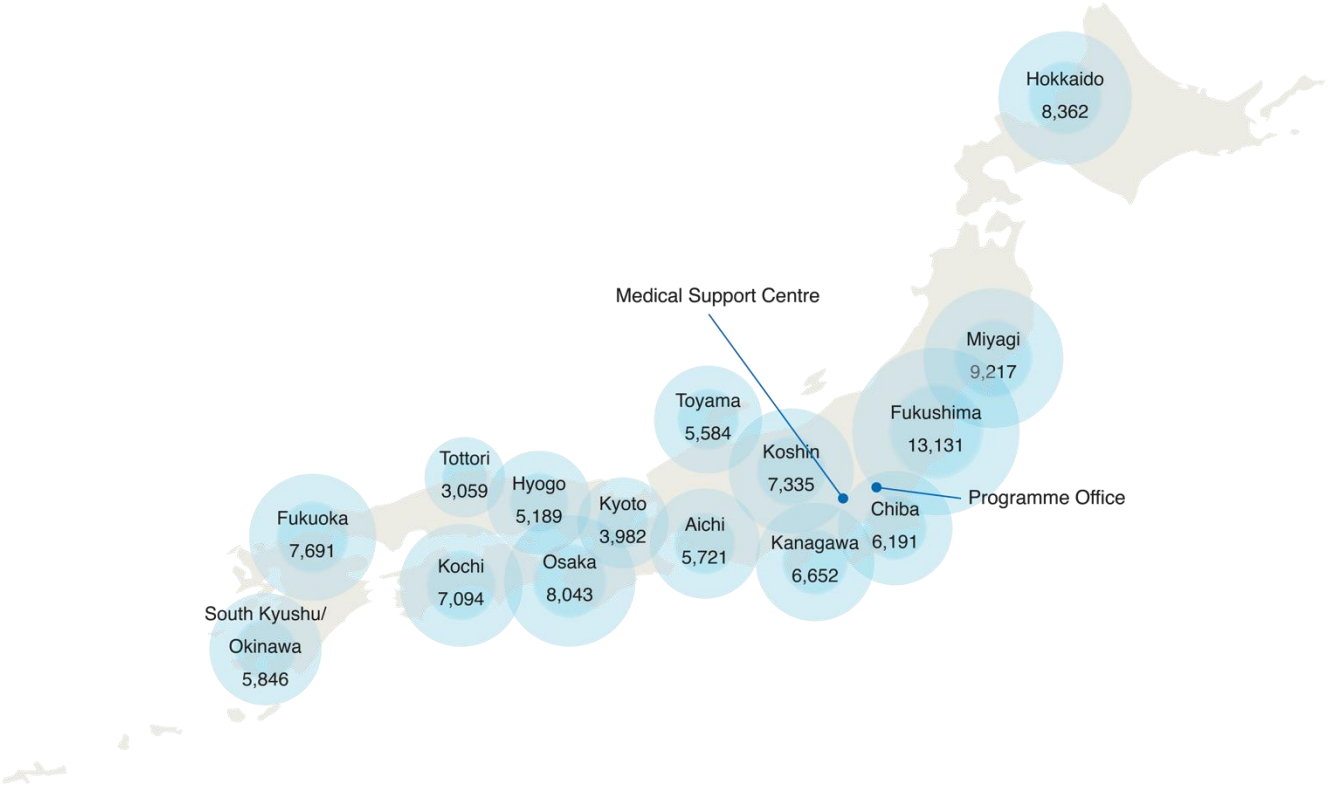


Figure 2: Programme Office, Medical Support Centre and Regional Centres and the number of participants

3.2 Follow-up programme

As a part of the Main Study, the participants (mothers) are asked to fill out questionnaires every 6 months after their children become 6 months old.

The response rate[3] for each questionnaire are presented in Table 6. As seen in the table, the total response rate has been maintained as over 80%, with some variance between different regional areas, though it decreases slightly as the study proceeded. We are going to make as much effort as possible to maintain high response rate.

The data collection for the Sub-Cohort Study began in November 2014. Participants at the age of 18 months have been receiving home visits for volatile organic compounds (VOCs) measurements, particulate matter collection and dwelling observation. Since April 2015, the participants has been administered a psychological developmental test (adjusted version of Kyoto Scale of Psychological Development), neuromotor test, paediatricians' examination and blood testing when they became 2 years old.

Table 6: Response rate for each questionnaire administration as of July 2019

Questionnaires	6 m	1 y	1.5 y	2 y	2.5 y	3 y	3.5 y
	84.1%	91.3%	89.2%	87.2%	85.6%	84.2%	81.7%
Questionnaires	4 y	4.5 y	5 y	5.5 y	6 y	7 y	G 1
	80.3%	78.5%	76.1%	77.4%	77.2%	76.7%	78.0%

[3] Response rate is calculated by the number of questionnaires sent back from the participants within 6 months after sending them divided by the total number of questionnaires sent to the participants

3.3 Collection and analyses of biospecimens

The collection of biospecimens during pregnancy and at birth was completed in the end of January 2015. The numbers of collected samples are listed in Table 7. The collected samples are stored in three different bio-repository facilities. In 2014, we started analysing mothers' blood samples during late pregnancy and 12,000 urine samples for metallic elements (lead, cadmium, mercury, manganese and selenium) and nicotine metabolites, respectively. Other measurements are listed in Table 8.

Table 7: Biological samples collected during pregnancy and at birth

Sample type	Participant		Number
Blood	Mother	Early pregnancy	91,935
		Mid–late pregnancy	97,979
		At birth	98,818
	Father		49,796
	Umbilical cord blood		87,802
	Child		94,841
Breast milk	Mother		89,364
Hair	Mother		78,719
	Child		94,990

Table 8: Biomonitoring progress

Sample	Target	Number	Year
Whole blood (mother, 2nd–3rd trimester)	Elements (Pb, Cd, Hg, Mn, Se)	95,811	2014–2017
Cord blood (sub-cohort)	Elements (Pb, Cd, Hg, Mn, Se)	3,897	2018
Urine (mother, 1st trimester)	Cotinine, 8-OHdG	96,490	2014–2017
Plasma (mother, 2nd–3rd trimester)	Perfluorinated alkyl substances (28 PFAS)	25,000	2017
Cord blood (sub-cohort)	Inorganic Hg and methyl Hg	3,897	2018
Urine (mother, 1st trimester)	Phenols (parabens, triclosan, benzophenone-3, nonylphenols, bisphenols, etc.)	10,000	2018
Urine (mother, 1st trimester)	Organophosphate pesticide metabolites (DMP, DEP, DMTP, DETP, etc.)	5,000	2018
Urine (mother, 1st trimester)	Phthalates (36 metabolites)	20,000	2019
Urine (mother, 1st trimester)	Neonicotinoid pesticides	20,000	2019

3.4 Data cleaning

The birth data was cleaned, frozen and distributed to the Regional Centres for analyses in April 2016. Data up to 1 year of age was frozen and distributed among JECS researchers in January 2018. The first 20,000 metallic element measurement data (lead, mercury, cadmium, manganese and selenium) was shared within JECS group in April 2017. The following data are being prepared: questionnaire data up to age 3; metallic element data

(95,811 maternal whole blood, 3,897 cord blood); nicotine and 8-OHdG in 96,490 maternal urine; home visit data at 1.5 and 3 years of age (~5,000); and medical examination and developmental test data at the age of 3 years (~5,000) and will be shared among JECS group in September 2019.

3.5 Publication

Considering the potential impact of the study results, JECS has publication and presentation rules. It requires data users to be registered by the Programme Office and authors are to submit the manuscript and presentation abstract to the Programme Office and obtain approval from the MOE for publication.

As of August 2019, 64 articles have been published in peer reviewed journals.

JECS publication:

Motoki N, Inaba Y, Shibazaki T, Misawa U, Ohira S, Kanai M, et al. Maternal Exposure to Housing Renovation During Pregnancy and Risk of Offspring with Congenital Malformation: The Japan Environment and Children's Study. Scientific Reports 2019. doi: 10.1038/s41598-019-47925-8.

Mezawa H, Aoki S, Nakayama SF, Nitta H, Ikeda N, Kato K, et al. Psychometric profiles of the Ages and Stages Questionnaires, Japanese translation. Pediat Int 2019. doi: 10.1111/ped.13990.

Nakayama SF, Espina C, Kamijima M, Magnus P, Charles M-A, Zhang J, et al. Benefits of cooperation among large-scale cohort studies and human biomonitoring projects in environmental health research: An exercise in blood lead analysis of the Environment and Child Health International Birth Cohort Group. Int J Hyg Environ Health 2019. doi: 10.1016/j.ijheh.2019.07.005.

Mitsuda N, Hosokawa T, Eitoku M, Fujieda M, Suganuma N. Breastfeeding and risk of febrile seizures in infants: The Japan Environment and Children's Study. Brain Dev 2019. doi: 10.1016/j.braindev.2019.07.001.

Iwama N, Metoki H, Nishigori H, Mizuno S, Takahashi F, Tanaka K, et al. Association between alcohol consumption during pregnancy and hypertensive disorders of pregnancy in Japan: the Japan Environment and Children's Study. Hypertens Res 2019;42:85–94. doi: 10.1038/s41440-018-0124-3.

Kobayashi S, Sata F, Murata K, Saijo Y, Araki A, Miyashita C, et al. Dose-dependent associations between prenatal caffeine consumption and small for gestational age, preterm birth, and reduced birthweight in the Japan Environment and Children's Study. Paediatr Perinat Epidemiol 2019;33:185–94. doi: 10.1111/ppe.12551.

Kigawa M, Tsuchida A, Miura K, Ito M, Tanaka T, Hamazaki K, et al. Analysis of non-respondent pregnant women who were registered in the Japan Environment and Children's Study: a longitudinal cohort study. BMJ Open 2019;9:e025562. doi: 10.1136/bmjopen-2018-025562.

Nakayama SF, Iwai-Shimada M, Oguri T, Isobe T, Takeuchi A, Kobayashi Y, et al. Blood mercury, lead, cadmium, manganese and selenium levels in pregnant women and their determinants: the Japan Environment and Children's Study (JECS). J Expo Sci Environ Epidemiol 2019. doi: 10.1038/s41370-019-0139-0.

Ito M, Takamori A, Yoneda S, Shiozaki A, Tsuchida A, Matsumura K, et al. Fermented foods and preterm birth risk from a prospective large cohort study: the Japan Environment and Children's study. Environ Health Prev Med 2019;24:25. doi: 10.1186/s12199-019-0782-z.

Hamazaki K, Tsuchida A, Takamori A, Tanaka T, Ito M, Inadera H. Dietary intake of fish and ω-3 polyunsaturated fatty acids and physician-diagnosed allergy in Japanese population: The Japan Environment and Children's Study. Nutrition 2019;61:194–201. doi: 10.1016/j.nut.2018.11.010.

Nagata C, Yang L, Yamamoto-Hanada K, Mezawa H, Ayabe T, Ishizuka K, et al. Complications and adverse outcomes in pregnancy and childbirth among women who conceived by assisted reproductive technologies: a nationwide birth cohort study of Japan Environment and Children's Study. BMC Pregnancy Childbirth 2019;19:77. doi: 10.1186/s12884-019-2213-y.

Komori K, Komori M, Eitoku M, Joelle Muchanga SM, Ninomiya H, Kobayashi T, et al. Verbal abuse during pregnancy increases frequency of newborn hearing screening referral: The Japan Environment and Children's Study. Child Abuse Negl 2019;90:193–201. doi: 10.1016/j.chiabu.2019.01.025.

Nishigori H, Obara T, Nishigori T, Ishikuro M, Sakurai K, Hoshiai T, et al. Preconception folic acid supplementation use and the occurrence of neural tube defects in Japan: A nationwide birth cohort study of the Japan Environment and Children's Study. Congenit Anom (Kyoto) 2019;59:110–7. doi: 10.1111/cga.12293.

Michikawa T, Yamazaki S, Ono M, Kuroda T, Nakayama SF, Suda E, et al. Fish consumption in early pregnancy and congenital gastrointestinal tract atresia in the Japan Environment and Children's Study. Br J Nutr 2019;121:100–8. doi: 10.1017/S0007114518002842.

Hirokawa K, Kimura T, Ikehara S, Honjo K, Sato T, Ueda K, et al. Associations between broader autism phenotype (BAP) and maternal attachment are moderated by maternal postpartum depression when infants are one month old: A prospective study of the Japan Environment and Children's Study. J Affect Disord 2019;243:485–93. doi: 10.1016/j.jad.2018.09.060.

Mezawa H, Tomotaki A, Yamamoto-Hanada K, Ishitsuka K, Ayabe T, Konishi M, et al. Prevalence of Congenital Anomalies in the Japan Environment and Children's Study. J Epidemiol 2019;29:247–56. doi: 10.2188/jea.JE20180014.

Oguri T, Ebara T, Nakayama SF, Sugiura-Ogasawara M, Kamijima M. Association between maternal blood cadmium and lead concentrations and gestational diabetes mellitus in the Japan Environment and Children's Study. Int Arch Occup Environ Health 2019;92:209–17. doi: 10.1007/s00420-018-1367-7.

Kobayashi S, Kishi R, Saijo Y, Ito Y, Oba K, Araki A, et al. Association of blood mercury levels during pregnancy with infant birth size by blood selenium levels in the Japan Environment and Children's Study: A prospective birth cohort. Environ Int 2019;125:418–29. doi: 10.1016/j.envint.2019.01.051.

Sugiura-Ogasawara M, Ebara T, Matsuki T, Yamada Y, Omori T, Matsumoto Y, et al. Endometriosis and Recurrent Pregnancy Loss as New Risk Factors for Venous Thromboembolism during Pregnancy and Post-Partum: The JECS Birth Cohort. Thromb Haemost 2019;119:606–17. doi: 10.1055/s-0039-1677733.

Hattori H, Kitamura A, Takahashi F, Kobayashi N, Sato A, Miyauchi N, et al. The risk of secondary sex ratio imbalance and increased monozygotic twinning after blastocyst transfer: data from the Japan Environment and Children's Study. Reprod Biol Endocrinol 2019;17:27. doi: 10.1186/s12958-019-0471-1.

Yamamoto M, Sakurai K, Eguchi A, Yamazaki S, Nakayama SF, Isobe T, et al. Association between blood manganese level during pregnancy and birth size: The Japan Environment and Children's Study (JECS). Environ Res 2019;172:117–26. doi: 10.1016/j.envres.2019.02.007.

Tsuchida A, Hamazaki K, Matsumura K, Miura K, Kasamatsu H, Inadera H, et al. Changes in the association between postpartum depression and mother-infant bonding by parity: Longitudinal results from the Japan Environment and Children's Study. J Psychiatr Res 2019;110:110–6. doi: 10.1016/j.jpsychires.2018.11.022.

Tsuji M, Koriyama C, Ishihara Y, Yamamoto M, Yamamoto-Hanada K, Kanatani K, et al. Associations Between Metal Levels in Whole Blood and IgE Concentrations in Pregnant Women Based on Data From the Japan Environment and Children's Study. J Epidemiol 2019. doi: 10.2188/jea.JE20180098.

Konishi M, Tomotaki A, Yamamoto-Hanada K, Mezawa H, Ayabe T, Ishitsuka K, et al. Sleep status varies by age among Japanese women during preconception and pregnancy in a nationwide birth cohort study [the Japan Environment and Children's Study (JECS)]. Sleep Biol Rhythms 2019;17:161–72. doi: 10.1007/s41105-018-0195-1.

Watanabe Z, Nishigori H, Tanoue K, Tanaka K, Iwama N, Satoh M, et al. Preconception dysmenorrhea as a risk factor for psychological distress in pregnancy: The Japan Environment and Children's Study. J Affect Disord 2019;245:475–83. doi: 10.1016/j.jad.2018.11.061.

Ishitsuka K, Yamamoto-Hanada K, Ayabe T, Mezawa H, Konishi M, Saito-Abe M, et al. Risky Health Behaviors of Teenage Mothers and Infant Outcomes in the Japan Environment and Children's Study: A Nationwide Cohort Study. J Pediatr Adolesc Gynecol 2019;32:146–52. doi: 10.1016/j.jpag.2018.10.009.

Michikawa T, Yamazaki S, Ono M, Kuroda T, Nakayama SF, Suda E, et al. Isoflavone Intake in Early Pregnancy and Hypospadias in the Japan Environment and Children's Study. Urology 2019;124:229–36. doi: 10.1016/j.urology.2018.11.008.

Morokuma S, Michikawa T, Kato K, Sanefuji M, Shibata E, Tsuji M, et al. Non-reassuring foetal status and neonatal irritability in the Japan Environment and Children's Study: A cohort study. Sci Rep 2018;8:15853. doi: 10.1038/s41598-018-34231-y.

Takami M, Tsuchida A, Takamori A, Aoki S, Ito M, Kigawa M, et al. Effects of physical activity during pregnancy on preterm delivery and mode of delivery: The Japan Environment and Children's Study, birth cohort study. PLoS One 2018;13:e0206160. doi: 10.1371/journal.pone.0206160.

Honjo K, Kimura T, Baba S, Ikehara S, Kitano N, Sato T, et al. Association between family members and risk of postpartum depression in Japan: Does "who they live with" matter? -The Japan Environment and Children's Study. Soc Sci Med 2018;217:65–72. doi: 10.1016/j.socscimed.2018.09.043.

Tsuji M, Shibata E, Morokuma S, Tanaka R, Senju A, Araki S, et al. The association between whole blood concentrations of heavy metals in pregnant women and premature births: The Japan Environment and Children's Study (JECS). Environ Res 2018;166:562–9. doi: 10.1016/j.envres.2018.06.025.

Mitsuda N, Eitoku M, Yamasaki K, Sakaguchi M, Yasumitsu-Lovell K, Maeda N, et al. Nausea and vomiting during pregnancy associated with lower incidence of preterm births: the Japan Environment and Children's Study (JECS). BMC Pregnancy Childbirth 2018;18:268. doi: 10.1186/s12884-018-1911-1.

Tanaka R, Tsuji M, Senju A, Kusuhara K, Kawamoto T. Dietary Differences in Male Workers among Smaller Occupational Groups within Large Occupational Categories: Findings from the Japan Environment and Children's Study (JECS). Int J Environ Res Public Health 2018;15:961. doi: 10.3390/ijerph15050961.

Iwai-Shimada M, Nakayama SF, Isobe T, Michikawa T, Yamazaki S, Nitta H, et al. Questionnaire results on exposure characteristics of pregnant women participating in the Japan Environment and Children Study (JECS). Environ Health Prev Med 2018;23:45. doi: 10.1186/s12199-018-0733-0.

Iwama N, Metoki H, Nishigori H, Mizuno S, Takahashi F, Tanaka K, et al. Blood pressure changes during twin pregnancies. J Hypertens 2018:1. doi: 10.1097/HJH.0000000000001846.

Yoshimasu K, Sato A, Miyauchi N, Tsuno K, Nishigori H, Nakai K, et al. Lack of association between receiving ART treatment and parental psychological distress during pregnancy: Preliminary findings of the Japan Environment and Children's Study. Reprod Biomed Soc Online 2018;5:5–16. doi: 10.1016/j.rbms.2017.09.002.

Saito M, Yamamoto-Hanada K, Pak K, Ayabe T, Mezawa H, Ishitsuka K, et al. Having small-for-gestational-age infants was associated with maternal allergic features in the JECS birth cohort. Allergy 2018;73:1908–11. doi: 10.1111/all.13490.

Tanaka R, Tsuji M, Asakura K, Senju A, Shibata E, Kusuhara K, et al. Variation in Men's Dietary Intake Between Occupations, Based on Data From the Japan Environment and Children's Study. Am J Mens Health 2018;12:1621–34. doi: 10.1177/1557988318780847.

Tanaka R, Tsuji M, Kusuhara K, Kawamoto T. Association between time-related work factors and dietary behaviors: results from the Japan Environment and Children's Study (JECS). Environ Health Prev Med 2018;23:62. doi: 10.1186/s12199-018-0753-9.

Baba S, Kimura T, Ikehara S, Honjo K, Eshak ES, Sato T, et al. Impact of intention and feeling toward being pregnant on postpartum depression: the Japan Environment and Children's Study (JECS). Arch Womens Ment Health 2018. doi: 10.1007/s00737-018-0938-7.

Sugiura-Ogasawara M, Ebara T, Yamada Y, Shoji N, Matsuki T, Kano H, et al. Adverse pregnancy and perinatal outcome in patients with recurrent pregnancy loss: Multiple imputation analyses with propensity score adjustment applied to a large-scale birth cohort of the Japan Environment and Children's Study. Am J Reprod Immunol 2018:e13072. doi: 10.1111/aji.13072.

Yoshida T, Matsumura K, Tsuchida A, Hamazaki K, Inadera H. Association between cesarean section and constipation in infants: the Japan Environment and Children's Study (JECS). BMC Res Notes 2018;11:882. doi: 10.1186/s13104-018-3990-5.

Morisaki N, Nagata C, Yasuo S, Morokuma S, Kato K, Sanefuji M, et al. Optimal protein intake during pregnancy for reducing the risk of fetal growth restriction: the Japan Environment and Children's Study. Br J Nutr 2018;120:1432–40. doi: 10.1017/S000711451800291X.

Mitsuda N, Eitoku M, Maeda N, Fujieda M, Suganuma N. Severity of Nausea and Vomiting in Singleton and Twin Pregnancies in Relation to Fetal Sex: The Japan Environment and Children's Study (JECS). J Epidemiol 2018. doi: 10.2188/jea.JE20180059.

Michikawa T, Nitta H, Nakayama SF, Yamazaki S, Isobe T, Tamura K, et al. Baseline Profile of Participants in the Japan Environment and Children's Study (JECS). J Epidemiol 2018;28:99–104. doi: 10.2188/jea.JE20170018.

Yamamoto-Hanada K, Ishitsuka K, Pak K, Saito M, Ayabe T, Mezawa H, et al. Allergy and mental health among pregnant women in the Japan Environment and Children's Study. J Allergy Clin Immunol Pract 2018;6:1421-1424.e2. doi: 10.1016/j.jaip.2017.12.006.

Hamazaki K, Takamori A, Tsuchida A, Kigawa M, Tanaka T, Ito M, et al. Dietary intake of fish and n-3 polyunsaturated fatty acids and risks of perinatal depression: The Japan Environment and Children's Study (JECS). J Psychiatr Res 2018;98:9–16. doi: 10.1016/j.jpsychires.2017.11.013.

Obara T, Nishigori H, Nishigori T, Metoki H, Ishikuro M, Tatsuta N, et al. Prevalence and determinants of inadequate use of folic acid supplementation in Japanese pregnant women: the Japan Environment and Children's Study (JECS). J Matern Neonatal Med 2017;30:588–93. doi: 10.1080/14767058.2016.1179273.

Nishigori H, Obara T, Nishigori T, Mizuno S, Metoki H, Hoshiai T, et al. Selective serotonin reuptake inhibitors and risk of major congenital anomalies for pregnancies in Japan: A nationwide birth cohort study of the Japan Environment and Children's Study. Congenit Anom (Kyoto) 2017;57:72–8. doi: 10.1111/cga.12202.

Nishigori H, Obara T, Nishigori T, Metoki H, Ishikuro M, Mizuno S, et al. Drug Use before and during Pregnancy in Japan: The Japan Environment and Children's Study. Pharmacy 2017;5:21. doi: 10.3390/pharmacy5020021.

Morita M, Go T, Hirabayashi K, Heike T, Study Group JE and C. Parental Condition and Infant Sex at Birth in the Japan Environment and Children's Study: A Test of the Trivers–Willard Hypothesis. Lett Evol Behav Sci 2017;8:40–4. doi: 10.5178/lebs.2017.63.

Nishigori H, Nishigori T, Sakurai K, Mizuno S, Obara T, Metoki H, et al. Pregnant Women's Awareness of Social Capital in the Great East Japan Earthquake-Affected Areas of Miyagi Prefecture: The Japan Environment and Children's Study. Disaster Med Public Health Prep 2017;11:355–64. doi: 10.1017/dmp.2016.150.

Yamamoto-Hanada K, Yang L, Ishitsuka K, Ayabe T, Mezawa H, Konishi M, et al. Allergic profiles of mothers and fathers in the Japan Environment and Children's Study (JECS): a nationwide birth cohort study. World Allergy Organ J 2017;10:24. doi: 10.1186/s40413-017-0157-0.

Muchanga SMJ, Yasumitsu-Lovell K, Eitoku M, Mbelambela EP, Ninomiya H, Komori K, et al. Preconception gynecological risk factors of postpartum depression among Japanese women: The Japan Environment and Children's Study (JECS). J Affect Disord 2017;217:34–41. doi: 10.1016/j.jad.2017.03.049.

Morokuma S, Shimokawa M, Kato K, Sanefuji M, Shibata E, Tsuji M, et al. Maternal sleep and small for gestational age infants in the Japan Environment and Children's Study: a cohort study. BMC Res Notes 2017;10:394. doi: 10.1186/s13104-017-2675-9.

Sakurai K, Nishigori H, Nishigori T, Mizuno S, Obara T, Iwama N, et al. Incidence of Domestic Violence Against Pregnant Females After the Great East Japan Earthquake in Miyagi Prefecture: The Japan Environment and Children's Study. Disaster Med Public Health Prep 2017;11:216–26. doi: 10.1017/dmp.2016.109.

Suzuki K, Shinohara R, Sato M, Otawa S, Yamagata Z. Association Between Maternal Smoking During Pregnancy and Birth Weight: An Appropriately Adjusted Model From the Japan Environment and Children's Study. J Epidemiol 2016;26:371–7. doi: 10.2188/jea.JE20150185.

Mizuno S, Nishigori H, Sugiyama T, Takahashi F, Iwama N, Watanabe Z, et al. Association between social capital and the prevalence of gestational diabetes mellitus: An interim report of the Japan Environment and Children's Study. Diabetes Res Clin Pract 2016;120:132–41. doi: 10.1016/j.diabres.2016.07.020.

Harada T, Taniguchi F, Onishi K, Kurozawa Y, Hayashi K, Harada T. Obstetrical Complications in Women with Endometriosis: A Cohort Study in Japan. PLoS One 2016;11:e0168476. doi: 10.1371/journal.pone.0168476.

Morokuma S, Shimokawa M, Kato K, Sanefuji M, Shibata E, Tsuji M, et al. Relationship between hyperemesis gravidarum and small-for-gestational-age in the Japanese population: the Japan Environment and Children's Study (JECS). BMC Pregnancy Childbirth 2016;16:247. doi: 10.1186/s12884-016-1041-6.

Takahashi F, Nishigori H, Nishigori T, Mizuno S, Obara T, Metoki H, et al. Fermented Food Consumption and Psychological Distress in Pregnant Women: A Nationwide Birth Cohort Study of the Japan Environment and Children's Study. Tohoku J Exp Med 2016;240:309–21. doi: 10.1620/tjem.240.309.

Watanabe Z, Iwama N, Nishigori H, Nishigori T, Mizuno S, Sakurai K, et al. Psychological distress during pregnancy in Miyagi after the Great East Japan Earthquake: The Japan Environment and Children's Study. J Affect Disord 2016;190:341–8. doi: 10.1016/j.jad.2015.10.024.

Michikawa T, Nitta H, Nakayama SF, Ono M, Yonemoto J, Tamura K, et al. The Japan Environment and Children's Study (JECS): A Preliminary Report on Selected Characteristics of Approximately 10 000 Pregnant Women Recruited During the First Year of the Study. J Epidemiol 2015;25:452–8. doi: 10.2188/jea.JE20140186.

Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, et al. Rationale and design of the Japan Environment and Children's Study (JECS). BMC Public Health 2014;14:25. doi: 10.1186/1471-2458-14-25.

Japan Environment and Children's Study (JECS)

Study Protocol (ver. 1.6)

Japan Environment and Children's Study Programme Office
National Institute for Environmental Studies

Statement of Compliance

This Study shall be conducted in accordance with its Protocol reviewed and approved by the institutional review boards (IRBs), complying with the Ethical Guidelines for Epidemiological Research (MEXT and MHLW) as well as the Ethical Guidelines for Analytical Research on the Human Genome/Genes (MEXT, MHLW and METI). The Principal Investigator shall assure that no deviation from or change to the Protocol will take place without prior approval from the IRBs, except when necessary to eliminate any immediate hazard(s) to the Study participants. Adjunct Study protocols shall be prepared by Regional Centres and subject to review and approval by an IRB to which each Regional Centre must report. When a new protocol is approved or the existing protocol is changed, the Regional Centres promptly shall report to the Steering Committee.

Table of Contents

List of Abbreviations

IRB	Institutional Review Board
JECS	Japan Environment and Children's Study
MEXT	Ministry of Education, Culture, Sports, Science and Technology
MHLW	Ministry of Health, Labour and Welfare
METI	Ministry of Economics, Trade and Industry
NIES	National Institute for Environmental Studies
MOP	Manual of Procedure/Miscellaneous Operation Procedure
MOE	Ministry of the Environment
SOP	Standard operating procedure

Overview

In March 2010, Ministry of the Environment (MOE) published a conceptual plan for the Japan Environment and Children's Study (JECS) that drafts a nation-wide birth cohort study on children's health and development. The goal of JECS is to identify environmental factors that affect children's health and development during the foetal period and/or in early childhood, in order to facilitate development of a better environmental risk management system. Specifically, JECS focuses on the effect of children's exposure to chemical substances. JECS examines hypotheses regarding to associations between environmental factors and children's adverse health outcomes in several different domains: Reproduction/pregnancy complications, congenital anomalies, neuropsychiatric disorders, immune system deficits/allergic responses and metabolic/endocrine system dysfunctions. JECS assesses the level of children's environmental exposures and measures variables that are relevant to health outcomes. Additionally, JECS also examines possible covariates and confounders including physical and social environment, genetic factors and behaviours.

JECS is operated in cooperation among several research institutions. The National Centre for JECS or Programme Office, which is situated in the National Institute for Environmental Studies (NIES), takes a directive role for JECS, such as preparing various standard operating procedures (SOPs), managing data and storing biological samples. The Medical Support Centre, which resides in the National Centre for Child Health and Development, supports the Programme Office with its medical expertise. The Programme Office and Medical Support Centre cooperate together with 15 Regional Centres that are located in universities and other research institutions. Regional Centres select their own study areas (i.e., a single or multiple administrative districts), taking account of their number of births, regional representativeness and level of potential environmental exposures. The Regional Centres are responsible for recruiting and maintaining study participants and gathering data in their selected study areas at each study phase.

The prospective participants of JECS are 100,000 children and their parents who live in designated study areas. JECS aims to recruit expecting mothers who have lived in the study areas and are expected to stay there for the next three years from January 2011. The children born to these mothers are followed until they reach 13 years of age. JECS is planned to continue until 2032, allowing five years of data analysis after the completion of data collection.

JECS consists of: 1) Main Study that includes all the participants recruited; 2) Sub-Cohort Study with 5,000 participants randomly extracted from the Main Study; 3) Pilot Study that examines validity and feasibility of study protocols before they are applied to the Main Study and 4) Adjunct Studies conducted by each or any combination of JECS organisation(s) using extramural funding targeting all or a part of the Main Study participants, which must be approved by MOE. In the Main Study, extensive biological sample collections are performed at a variety of time points. The biologi-

cal samples include blood and urine from mothers during pregnancy and at birth; cord blood at delivery; hair and breast milk from mothers at one-month visits; hair from children at one month, and if accessible, blood of fathers. Blood and urine samples from selected children are collected in the Sub-Cohort Study. Concentrations of different chemical agents in these collected biospecimens are measured, in order to estimate the degree of chemical exposures of the study participants. The biospecimens are also utilized to assess biomarkers of the health outcomes such as allergies as well as to conduct genetic analyses. Questionnaire surveys and physical examinations are also conducted in order to enhance the assessment for environmental exposure, health outcomes and covariates/confounders.

Amendment: The accident of the Fukushima Daiichi Nuclear Power Plant happened in March 2011. The study area of Fukushima Regional Centre is expanded due to the increasing national concern over the impact of radioactivity on health.

1 Organisation

1.1 Principal Investigator

The Principal Investigator of JECS is appointed as a chairperson of the JECS Steering Committee.

1.2 Programme Office

The Japan Environment and Children's Study (JECS) Programme Office is established in the National Institute for Environmental Studies. The Programme Office takes a directive role for JECS, including preparing various SOPs; accumulating and maintaining data collected by Regional Centres; storing and handling biological and environmental specimens and performing chemical analyses on the specimen. The Programme Office also provides administrative and technical support for Regional Centres and is responsible for risk management and public communication.

1.3 Medical Support Centre

Medical Support Centre is established in the National Centre for Child Health and Development. The Medical Support Centre provides the Programme Office with medical expertise, specifically, by developing/selecting health outcome measures; standardising the measurement procedures; preparing manuals for the measurements and training personnel who are responsible for gathering data of health outcome variables at each Regional Centre. The Medical Support Centre provides Regional Centres with advices on medical issues.

1.4 Regional Centres

The Regional Centres are responsible for recruiting study participants in respective study areas; collecting data from the participants at each study phase and collaborating with local governments and local health care providers (defined as 'cooperating health care providers'). As a part of recruitment and data collection, the Regional Centres directly contact the study participants in order to inform them the study protocols; obtain the written consent from them; register the participants; collect biospecimens; gather the information from medical records and carry out questionnaire surveys and environmental measurements.

The following list presents 15 Regional, their designated study areas, planned sample sizes and corresponding organisations (

Table 1).

Table 1: Regional Centres, study areas, planned sample sizes and corresponding organisations

Regional Centres	Study Area	Planned Sample Size	Organisation
Hokkaido	Sapporo (Kita-ku and Toyohira-ku), Asahikawa, part of Kitami, Oketo, Kunneppu , Tsubetsu and Bihoro	8,250	Hokkaido University Sapporo Medical University Asahikawa Medical University The Japanese Red Cross, Hokkaido College of Nursing
Miyagi	Kesennuma, Minamisanriku, Ishinomaki, Onagawa, Osaki, Wakuya, Misato, Kami, Shikama, Kurihara, Tome, Iwanuma, Watari and Yamamoto	9,900	Tohoku University
Fukushima	Fukushima Prefecture	15,900	Fukushima Medical University
Chiba	Kamogawa, Minamiboso, Tateyama, Kyonan, Katsuura, Isumi, Onjuku, Ootaki, Kisarazu, Sodegaura, Futtsu, Kimitsu, Ichimiya and Chiba (Midori-ku)	6,400	Chiba University
Kanagawa	Yokohama (Kanazawa-ku), Yamato and Odawara	6,650	Yokohama City University
Koshin	Kofu, Chuo, Koshu, Yamanashi, Fujiyoshida, Ina, Komagane, Tatsuno, Minowa, Iijima, Minamiminowa, Nakagawa and Miyada	7,250	University of Yamanashi Shinshu University
Toyama	Toyama, Kurobe, Uozu, Namerikawa, Asahi and Nyuzen	5,700	University of Toyama
Aichi	Ichinomiya and Nagoya (Kita-ku)	5,850	Nagoya City University
Kyoto	Kyoto (Sakyou-ku and Kita-ku), Kizugawa and Nagahama	3,850	Kyoto University Doshisha University
Osaka	Kishiwada, Kaizuka, Kumatori,	8,000	Osaka University

	Izumisano, Tajiri, Sennan, Hannan, Misaki and Izumi		Osaka Medical Centre Research Institute for Maternal and Child Health
Hyogo	Amagasaki	5,600	Hyogo College of Medicine
Tottori	Yonago, Sakaiminato, Daisen, Houki, Nanbu, Kofu, Hino, Nichinan and Hiezu	3,000	Tottori University
Kochi	Kochi, Nankoku, Shimanto, Yusuhara, Kohnan, Kami, Sukumo, Tosashimizu, Kuroshio, Ohtsuki and Mihara	7,000	Kochi University
Fukuoka	Kitakyushu (Yahatanishi-ku) and Fukuoka (Higashi-ku)	7,600	University of Occupational and Environmental Health Kyushu University
South Kyushu/ Okinawa	Minamata, Tsunagi, Ashikita, Amakusa, Reihoku, Kami-Amakusa, Hitoyoshi, Nishiki, Asagiri, Taragi, Yunomae, Mizukami, Sagara, Itsuki, Yamae, Kuma, Nobeoka and Miyakojima	5,750	Kumamoto University University of Miyazaki University of the Ryukyu

1.5 Steering Committee and Advisory Committees

The Steering Committee is established by the Programme Office and formed by representatives from the Programme Office, Medical Support Centre, Regional Centres and the MOE. The Principal Investigator of JECS chairs the Steering Committee. The Steering Committee is the highest decision making body of the JECS study protocol. Under the Steering Committee, subcommittees, such as advisory committees, the ethics committee and liaison committees are organized as appropriate. The Steering Committee receives advices and recommendations from the Project Evaluation Committee externally established by the MOE that monitors the operation of JECS from scientific and ethical perspectives.

2 Background

There has been a growing concern regarding the effects that environmental pollution posed to children, especially the vulnerability of children to harmful substances in the environment, throughout the world. In 1997, the Miami Declaration on Children's Environmental Health was adopted at the G8 Environment Ministers' Meeting in Miami. In late 1990's, Denmark, Norway and the United States commenced large-scale epidemiological studies on approximately 100,000 children to investigate the effects of environmental factors on children's health and development. In 2009, children's environmental health was highlighted again at the G8 Environment Ministers' Meeting held in Syracuse, Italy, where ministers agreed to cooperate in scientific research to push this movement forward.

Meanwhile, in August 2006, the MOE held a conference on children's environmental health. The conference specifically focused on children's vulnerability to environmental hazards. According to the report from the conference, children tend to have a unique pattern of chemical exposure due to their physical characteristics (e.g., metabolic disposition and toxicokinetics) and behavioural characteristics (e.g., staying close to floor, consuming more fruit and milk compared to adults). The report also indicated that children are possibly more vulnerable to environmental hazards than adults because of their immature physiological and biochemical function. These emphasize the importance of investigating effects of environmental hazards on children.

To evaluate the impact of environmental factors on human health, a great deal of research has been performed using laboratory animals. However, the findings of such studies cannot always be extrapolated to humans due to the difference in physiological and morphological features. In contrast, epidemiological research enables us to directly observe the effects of environmental factors on humans. (Report of the Conference on Epidemiological Study of Children's Environmental Health, March 2008).

In April 2008, MOE organized the Expert Group on the Epidemiological Research for Children's Environmental Health (later converted to the JECS Working Group) and started planning a new nation-wide epidemiological study. After small pilot studies were conducted at several locations to examine the appropriateness and feasibility of the study protocols, in March 2010, the Working Group published a conceptual plan for a large-scale birth cohort study covering all areas of Japan. This JECS Protocol is developed in accordance with the draft conceptual plan.

3 Study Objectives

The primary objective of JECS is to reveal environmental factors that affect children's health and development. Specifically, JECS aims to evaluate the effects of exposure to chemical substances during the foetal stage and/or in early childhood on children's health and development, which would eventually lead to better environmental risk assessment and management system. Children show a rapid and considerable development during foetal period and early and middle childhood, and as a result, their health status frequently changes. Additionally, exposure to certain environmental factors during foetal period and childhood may affect their health. JECS is designed as a prospective birth-cohort study that follows participating children from foetal period until they reach 13 years of age.

JECS holds five major domains of research hypotheses (Table 2). In order to test these hypotheses, in addition to chemical exposures, various possible confounders and modifiers (such as physical, genetic, social and lifestyle related factors) are measured through environmental measurement and questionnaire survey.

Table 2: Research hypotheses

Pregnancy/reproduction	・ Parents' (mother and father) exposure to chemical substances in the environment affects the sex ratio of their newborn. ・ Exposure to chemical substances in the environment causes abnormal pregnancy. ・ Exposure to chemical substances in the environment causes abnormal development of foetuses and neonates.
Congenital anomalies	・ Exposure to chemical substances in the environment is related to the incidence of congenital anomalies. ・ Congenital anomalies are caused by the combined effects of genetic susceptibility and exposure to chemical substances in the environment.
Neuropsychiatric development	・ Exposure to chemical substances in the environment during foetal period and/or in early childhood, either alone or in combination with genetic susceptibility, is related to later diagnoses of developmental disorders and/or other neuropsychiatric disorders. ・ Exposure to chemical substances in the environment during foetal period and/or in early childhood, either alone or in combination with genetic susceptibility, is related to later quality of

	neuropsychiatric development and development of neuropsychiatric symptoms.
Immune system/allergy	・ Exposure to chemical substances in the environment during foetal period and/or in early childhood is related to later development of allergic disease.
Metabolism/endocrine system	・ Exposure to chemical substances in the environment during foetal period and/or in early childhood is related to later development of obesity, insulin resistance and type 2 diabetes mellitus. ・ Exposure to chemical substances in the environment during foetal period and/or in early childhood is associated with later bone mass and bone density. ・ Exposure to chemical substances in the environment during foetal period and/or in early childhood influences physical growth. ・ Exposure to chemical substances in the environment during foetal period and/or in early childhood is related to later degree of sexual maturation and sex differentiation of the brain. ・ Exposure to chemical substances in the environment during foetal period and/or in early childhood has a significant impact on later thyroid function.

Regarding to paediatric cancers, no hypothesis is proposed in JECS since the cohort size of 100,000 is not considered large enough to secure the sufficient number of cases for statistical examination of the relationship between exposure to environmental factors and development of paediatric cancers. However, JECS collects the cancer data and participates in the International Childhood Cancer Cohort Consortium (I4C) that aims to pool multiple cohort data of childhood cancers for further analyses.

4 Study Areas and Participants

4.1 Selection of Study Areas

Each Regional Centre selects its own study areas. The study area of JECS is defined as geographical areas where participating pregnant women reside. A study area consists of one or several local administrative units (e.g., city and town). Each Regional Centre selects one or more study area(s) on the basis of the number of births, regional representativeness and level of potential exposures to environmental pollutants.

4.2 Selection of Study Participants

The participants are pregnant women who meet all of the inclusion criteria but not the exclusion criteria and their children. The children's fathers are registered as participants only when the mothers (or children after birth) participate in the study.

4.2.1 Inclusion criteria

1) A pregnant woman whose expected delivery date must be between 1 August 2011 and 31 March 2014
2) A pregnant woman must reside in one of the study areas selected by Regional Centres at the time of the recruitment and be expected to reside continually in Japan for the foreseeable future
3) A pregnant woman must visit a cooperating health care providers selected by a Regional Centre or local government offices to obtain a Mother-Child Health Handbook in a study area during the recruiting period

4.2.2 Exclusion criteria

1) A pregnant woman does not consent to participate in the study
2) A pregnant woman shows difficulty in comprehending the study procedures or filling out the questionnaires without support
3) A pregnant woman is reportedly not accessible at the time of delivery (e.g. a woman who plans to give birth outside the study area)

4.3 Method of Recruitment

The recruiting period is from January 2011 to March 2014. However, the recruitment for the participating child's father is attempted even after March 2014 until his child completes one-month check-up after birth.

Regional Centres working together with cooperating health care providers are responsible for recruiting participants. The participants (pregnant women, their partners and children) are selected so that they can represent the population residing in the study area. Either or both of the following two recruitment methods are applied.

4.3.1 Recruitment through cooperating health care providers

Regional Centres request cooperation from all of the health care providers that pregnant women living in the study areas possibly visit for prenatal examination and/or delivery. All the health care providers that have agreed on this study will be designated as cooperating health care providers. All the pregnant women living in the study areas who visit the cooperating health care providers are asked to participate in the study.

4.3.2 Recruitment through local government offices

In cooperation with local governments, when pregnant women living in the study areas apply for the Mother and Child Health Handbook (an official booklet given complimentary to all expecting mothers in Japan when they get pregnant in order to receive municipal services for pregnancy, delivery and childcare) at the local government offices, Regional Centres provide them with the information about JECS and ask for their participation. When the pregnant woman shows interest in the study, field staff from the Regional Centres ask her which health care provider she would visit for prenatal care and delivery. If the health care provider is designated as a cooperating health care provider, the pregnant woman is asked to participate in the study. If possible, informed consent is obtained at the same time when the Mother and Child Health Handbook is issued at a local government office.

JECS aims to recruit more than 50% of all pregnant mothers who reside in the study areas during the recruitment period.

4.4 Early Termination of Participation

Effort of following participants shall be terminated when the following incidents happen to the participating children:

1) Miscarriage
2) Stillbirth
3) Death of participating children

At these times, the children's parents are also excluded from the study. The corresponding Regional Centres need to collect necessary information about the termination and resister them before termination.

5 Study Design

5.1 Main Study

The Main Study is conducted with all the participants recruited by all the Regional Centres, and its content is nationally unified.

5.2 Sub-Cohort Study

The participants of the Sub-Cohort Study are randomly extracted from those of the Main Study at all the Regional Centres. The Sub-Cohort Study includes extended outcome and exposure assessments that are practically difficult to be administered in the Main Study because of its size. The written consent to the protocol of the Sub-Cohort Study is obtained separately from that of the Main Study. The sample size of the Sub-Cohort Study is 5,000 or 5% of the Main Study.

5.3 Adjunct Study

Adjunct Studies can be proposed and conducted by the Programme Office, Medical Support Centre, Regional Centres, or any combination of them using extramural funding. Adjunct Studies may include either all or a part of the Main Study participants. Proposals for Adjunct Studies need to be approved by MOE, ensuring that they do not interfere with the conduct of the Main Study and Sub-Cohort Study. The proposal of an Adjunct Study is submitted to the Steering Committee in advance of MOE's review.

6 Assessment/Measurement of Health Outcomes and Exposure

This section describes procedures for the assessment of health outcomes as well as environmental and genetic factors, and other related factors.

6.1 Assessment of Health Outcomes

On the following list are the outcome variables measured in the Main Study and the Sub-Cohort Study. JECS sets up SOPs that illustrate the outcomes measurement methods and procedures. Priority health outcomes are listed in Table 3.

Table 3: Priority health outcomes

Pregnancy/reproduction	Sex ratio, abnormal pregnancy, miscarriage, stillbirth, preterm delivery, birth weight, physical development after birth (e.g., motor function, kidney function, and lung function)
Congenital anomalies	Hypospadias, cryptorchidism, cleft lip and palate, intestinal atresia, ventricular septal defect, chromosome aberration
Neuropsychiatric developmental disorders	Developmental delay or deviation (mental retardation and other cognitive difficulties), autism spectrum disorder, learning disorder (LD), attention deficit hyperactivity disorder (ADHD), mental disorders, and other symptoms and behavioural characteristics
Immune system disorders	Food allergy, atopic dermatitis, asthma, allergic rhinitis, Kawasaki disease
Metabolic and endocrine system disorders	Abnormal glucose tolerance, obesity, effects on reproductive organs, genital dysplasia, sex differentiation of the brain
Childhood tumours	Leukaemia, brain tumours

6.2 Exposure Measurement

6.2.1 Biomonitoring

Analysing chemical substances and their metabolites in biospecimens is a major instrument for JECS exposure measurements besides questionnaire and modelling (ambient air and house dust measurement for Sub-Cohort Study). Chemical substances for evaluation are selected from the substances that easily accumulate in the human body; those that are known to easily pass through the placenta; those that children are often exposed to; and those that are of great public concern. To identify critical win-

dows of exposure, biological specimens (e.g. blood and urine) are collected from mothers twice during the pregnancy (early and mid–late). Umbilical cord blood samples are also collected at the time of birth. Additionally, breast milk samples are collected during lactation period. Hair samples from mothers and children are also collected and analysed specifically for detecting mercury. Since previous studies have indicated that fathers' exposure to chemical substances has certain impacts on their children's health, blood samples are collected from fathers when accessible. The chemical substances planned to be analysed for are listed in Appendix.

6.2.2 Ambient Measurement and Modelling

Besides biomonitoring, direct environmental measurements and modelling are used for air pollutant, indoor contaminants and radioactivity.

6.2.3 Genetic Analyses

JECS understands the importance of phenotypic difference both for exposure and health effect variation. The detailed study protocol (including analysis procedures) for genetic analyses will be prepared in future and reviewed for approval by IRBs. Participants will be informed the protocol and their consent will be re-taken before conducting genetic analysis.

6.2.4 Covariates and Potential Confounders

A series of questionnaires are used to measure covariates and potential confounders including demographic variables (e.g. residential address, education, employment, house-hold income), lifestyle factors (e.g. stress level, diet, smoking and drinking habits, exercise, sleep), physical environment (e.g., heat, ionizing radiation, housing condition, and neighbourhood), social/psychological factors (e.g., personality, social support), medical history (including pregnancy history) and medical history of family members.

6.3 Study Schedule

Table 4 shows the overall schedule of the Main Study and Sub-Cohort Study. JECS is planned to continue until 2032, allowing five years for data analysis after all the participating children reach 13 years

of age.

During their pregnancy, the data of the enrolled mothers are collected three times, once for each trimester (Table 3). After the mothers give birth, questionnaires are sent out to them every 6 months, taking account of the speed of the children's growth and development. Meanwhile, the information filled in the Mother and Child Health Handbook is transcribed to gather additional data regarding the children's growth and development.

Table 4: Study Milestones

Data collection Timing	Data collection method (Main Study)	Data collection method (Sub Study)
At recruitment (first trimester)	Medical record Questionnaire Biospecimen (Mother: blood (30 ml) and urine (50 ml), Father: blood (30 ml))	
Second and third trimester	Questionnaire Biospecimen (Mother: blood (30 ml) and urine (50 ml))	
At delivery	Medical record Biospecimen (Child: Umbilical cord blood (20–35 ml))	
Within a few days after birth (during hospitalization)	Biospecimen (Mother: blood (20 ml), hair (2 mg), Child: dried blood spot)	
1 month old	Medical record Questionnaire Biospecimen (Mother: breast milk (20 ml); Child: hair (2 mg))	
6 months old	Questionnaire	
1 year old	Questionnaire	
1.5 years old	Questionnaire	Environmental measurements
2 years old	Questionnaire	Developmental test Medical check (blood test, skin examination, etc.)

2.5 years old	Questionnaire	
3 years old	Questionnaire	Environmental measurements
3.5 years old	Questionnaire	
4 years old	Questionnaire	Developmental test Medical check (blood test, skin examination, etc.)
4.5–5.5 years old	Questionnaire (once every 6 months)	
6–12 years old	Questionnaire (one at birthday and the other at the middle of a school year) Transcription of school health examination results Deciduous teeth collection	Developmental/Neuropsychological test and/or interviews (at 8, 10 and 12 years old) Medical checks [blood test (10 ml), physical measurements, etc. at the age of 6,8,10 and 12 years] Personal exposure measurement (VOCs and aldehydes)
8 years old (Second grade)	Developmental tests (Computer assisted tests: CAT) Physical measurements Urine collection (~30 ml)	
12 years old (Sixth grade)	Paediatric examination Developmental tests (CAT) Physical measurement Biospecimen [Child: urine (50 ml) and possibly blood (under consideration)]	

Note: The planned analytical parameters for biospecimens are presented in the Appendix. As necessary, additional data collection shall be conducted to gather participants' information about several specific diseases in more detail, referring to their medical record and/or school record. Questionnaires are filled in by the child's mother, except for at the recruitment at which they are filled by both father and mother, separately.

6.4 Following Participants

The participating children are followed until they reach the age of 13 years. The target retention rate is 80% or greater. Each Regional Centre is responsible for gathering data from the participants whom it recruited, even when the participants move outside of their study areas in the middle of the study. However, if their participant moves to an area covered by another Regional Centre, the corresponding Regional Centre shall take over the role of following this participant, continuing plausible parts of the study. If their participant becomes out of reach through phone call or mailing in the middle of the study, the responsible Regional Centre needs to make every possible effort (e.g., accessing the registration data of the local government) to continue to follow the participant. If the participant is found to be completely inaccessible after every effort is made, she/he is considered to be dropped out from the study.

Information about child's birth and the date of birth is gathered through medical record at the time of delivery. The information regarding pregnancy and delivery (e.g., duration of pregnancy, birth weight) is confirmed through referral of the Mother and Child Health Handbook. When a child's birth record is missing or a child is stillborn, the information is collected through the reference of the Resident Registry and/or the report of Vital Statistics in cooperating with national and local governments. These official records are also utilized when participants (children, mothers, and fathers) decease, in order to verify their deaths and find out the reason of the deaths.

Changes in the residence of participants is informed through direct notifications from participants or returned mails. When participants become unreachable, the Resident Registry is referred to identify their current residential place.

The changes in demographic status of the participants, such as marital status of the mothers/fathers (divorce, remarriage, becoming a widow) and legal guardian of the participating children, are notified by participants directly and confirmed by reference of the Resident Registry as necessary.

6.5 School age examination

6.5.1 Second grade examination

A participant (child) at the age of 8 years (second grade at elemental school) is subject to the second-grade examination. A guardian of the participant receives detailed information about the examination. After the consent is given, the examination is conducted on the second-grade participant. The examination includes developmental tests using a computer assisted testing (CAT) system, physical measurement and urine collection (~30 ml).

6.5.2 Sixth grade examination

A participant (child) at the age of 12 years (sixth grade at elemental school) is subject to the sixth-grade examination.

7 Ethics and Protection of Participants' Rights and Information

7.1 Institutional Review Board (IRB)

The study's protocol and procedure for handling the collected individual data including biospecimens complies with the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by MEXT and MHLW. If genetic analyses are conducted as a part of the study, they should also comply with the Ethical Guidelines for Analytical Research on the Human Genome/Genes established by METI, MEXT and MHLW. The protocols of the Main Study and Sub-Cohort Study are submitted to the Review Committee for Epidemiological Studies (organised by the Ministry of Environment Ethics Committee) and the Ethical Committee for Medical Studies within the National Institute for Environmental Studies, to obtain their approval. Subsequently, the protocols are reviewed by each Regional Centre's IRB.

Organisations that conduct the Adjunct Studies are responsible for obtaining approvals from each IRB, the results of which are reported to the Steering Committee of JECS.

7.2 Data Management System

All necessary measures will be taken to ensure that study participants' privacy and confidentiality is protected in accordance to the guidelines presented in the Section 7.1.

All the collected data are stored in an electronic data management system (DMS) maintained by the Programme Office. The DMS is located in the facility with physical and technical safety management system complying with the Information Security Policy of Ministry of the Environment (ver. 4, August 2010). The following data are separated with each other for their storage: participants' personally identifiable information; de-identified or coded data collected through questionnaires, testing, home visits and laboratory analyses; and the de-coding table that are used to link the de-identified/coded data with personally identifiable information. Each Regional Centre has a privilege of accessing to all the data it has collected. The Programme Office is responsible for modifying and deleting the stored data when necessary. To prevent personally identifiable information from unintentional disclosure, the access to the DMS is limited to selected and trained personnel within the Programme Office, Medical Support Centre and Regional Centres. The rooms that host DMS terminals are maintained locked, allowing only the designated personnel to enter the rooms. The printed

documents (e.g., consent forms) containing personally identifiable information are stored in lockable cabinets until the end of the study period.

At the Programme Office, Medical Support Centre, and Regional Centres, system administrators of personally identifiable information are appointed from among those who have a profession-related confidentiality obligation but are not participating in JECS. Personnel who are given rights to access personally identifiable information at the Programme Office, Medical Support Centre, and Regional Centres have to submit a written agreement regarding protection of personally identifiable information to the system administrator of the respective institution.

7.3 Informed Consent

The participation of the children is proceeded preferably after their parents with custody (both father and mother or mother if she has sole custody) fully understand the contents of the study. The agreement on study participation of children and mother is obtained from pregnant mothers. For their partners (fathers), the consent from them is also obtained after providing them with the information about the JECS study protocol. The information collection from mother or father is carried out after receiving consent from them respectively.

7.3.1 Informed Consent Procedure

The Regional Centre staff explain about the study to the participants on the face-to-face basis and obtain written consent to the study protocol. The staff who are allowed to take this role are those who have completed the mandatory training and are designated as a research coordinator (RC) of JECS. The training is held by the Programme Office. The RCs hold a licensure/certificate of an occupation with legal obligation of confidentiality (e.g. doctors, nurses, midwives, etc.) or sign a nondisclosure agreement with the director of the institution they belong to. All Regional Centres use the same informed consent form provided by the Programme Office.

The RCs explain every element of the informed consent form to the participants face-to-face using easily understandable verbal expressions. The consent document must be signed by the participant after they fully understand all of the following aspects of the study and agree upon them:

a) Purpose of the study

b) Methods of the study

c) Eligibility for the participation

d) Duration of the study

e) Potential benefits

f) Potential risks and discomforts

g) Assurance of privacy protection and confidentiality of records and data

h) Usage and storage of collected data

i) Potential outcomes of the study

j) Voluntary participation and withdrawal

k) Compensation

l) Contact information

When any new research procedures are added to the study protocol (e.g., blood collection from children), the participants are informed and a new consent are obtained from the legal guardians of the participating children. When the children become mature enough to understand the verbal explanation of the new procedure, they will also be informed about the study procedure. The informed consent documents are duplicated and maintained by both the participants and the Regional Centres until the end of the study.

7.3.2 Participant withdrawal

When a withdrawal request is received from a participant, the request is shared with the Programme Office and the responsible Regional Centre. Withdraw procedure must be formally proceeded by obtaining a written form of withdrawal document from the participating children or their legal guardian. Participant's survey responses, clinical and biochemical data, and biological specimens are appropriately processed or discarded according to the participant's/legal guardian's request. Upon completion of the withdrawal procedure, the participant or the legal guardian is informed by the written from.

7.3.3 Informed Assent

When child reaches the age that she/he comprehends Japanese language, we provide the child with the information about the study in a plain language and try to obtain the understanding of the study content. In JECS, we obtained consent from a mother participant to the study protocols on behalf of her child, which is considered sufficient in accordance to the current ethics guidelines in Japan. On the other hand, JECS involves a participating child in the study for a long period of time and provides them with little to no benefits. Thus, we try our best to inform the child about procedures at each phase of the study and obtain their assent. This is considered important for the child to agree on the

long-term engagement.

When the participating child become a certain age, e.g. 16 years old in accordance with the guideline, we will inform the child about invasive procedures such as phlebotomy and obtain consent from them.

7.4 Long Term Storage of Biospecimens and Data

The Programme Office maintains a part of biospecimens including blood, cord blood, urine, breast milk, and hair collected from the participating mothers, their children, and the children's fathers, for additional analyses (e.g., gene analyses) that will be planned and conducted in future. The biospecimens are stored in a long-term storage facility located in the NIES.

All the data and biospecimen collected from the participants are stored until 2032, 5 years after completion of the data collection. When JECS is determined to be continued beyond 2032, duration of the data storage will also be extended as long as the study lasts. The possible extension of data and biospecimen storage period is also documented in the consent form. The data and biospecimen are stored and maintained in the condition of anonymous yet traceable.

Specific rules and procedures are set to provide the collected data and biospecimen to researchers/research institutions that plan to use them for other studies. The special sub-committee established in the Steering Committee examines each application and determines whether the data/biospecimen should be provided. Due to the fact that the collected biospecimens are precious and limited, the sub-committee evaluates each study proposal on strict standards, such as the degree of contribution of the study to JECS, and determines which study should have priority to receive the biospecimens. The data/biospecimens will be provided not only to researchers/research institutions who are members of JECS research group, but also to those who are not, after being anonymized by removing personally identifiable information from the original data.

Additionally, the MOE plans to provide data/biospecimens after the completion of JECS, establishing data archives and biospecimen bank. All of these possible future plans are included in the consent form.

7.5 Genetic Analyses and Counselling

When genetic analyses are determined to be conducted, the procedure of disclosing their outcomes will be reviewed by NIES IRB. When the outcome is shared with the participants, qualified physicians specializing in clinical genetics or certified genetic counsellors shall be appointed as supervisors in charge.

7.6 Information Protection and Communication

Researchers and staff involved in JECS make every effort to protect its participants from any risks and prevent them from suffering from any disadvantages caused by participation of the study.

The result derived from the analyses of questionnaires and biological specimens are actively shared with the participants upon their agreement in the consent form.

When JECS uncovers clinically relevant but unexpected findings, the Steering Committee sets up a sub-committee to examine and determine the contents of the finding that should be reported to the participants and the reporting procedure.

8 Sample size

The number of the participants for the Main Study is 100,000 (Table 5). This number is considered sufficient to evaluate the effect of an environmental variable with the relative risk 1.3 on development of a disease/health outcome with prevalence rate of approximately 10% (e.g., infantile obesity and allergic disease), with sufficient statistical power when both outcome variable and environmental variable are coded binary (presence/absence). This number of participants also allows us to test the effect of environmental variables with the relative risk 2.0 or greater on development of disease/health outcome variable with prevalence rate of 1.0 % or less.

The number of participants for the Sub-Cohort Study is set as 5,000, which is sufficient to test hypotheses regarding to the association between environmental variables and diseases with high prevalence rate, such as obesity and allergic diseases.

Table 5: Sample sizes necessary to test hypotheses statistically (Conditions: significance level = 5%, statistical power = 80%, relative risk=2.0, statistical test = adjusted Chi-square test (one-sided))

Name of disease	Prevalence	Number per 100,000	The percentage of individuals with a high level of exposure to a certain chemical substance				
			1%	3%	5%	10%	25%
Obesity	10%	10,000	8,100	***28,34***	***1,780***	***1,010***	***580***
Atopic dermatitis (5 years old)	3.8%	3,770	23,200	8,101	***5,080***	***2,860***	***1,632***
ADHD (5 years old)	3%	3,000	29,600	10,367	6,500	***3,660***	***2,088***

Asthma (5 years old)	2.4%	2,400	37,300	13,034	8,200	***4,610***	***2,624***
Cryptorchidism	0.7%	700	130,600	45,634	28,680	16,110	9,164
Down's syndrome	0.1%	100	921,100	321,667	202,160	113,510	64,536
Hypospadias	0.05%	50	1,843,400	643,700	404,580	227,150	129,140
Type 1 diabetes mellitus	0.001%	1	92,221,800	32,203,934	20,240,500	11,363,740	6,460,364

9 Statistical Analysis

As outcome variables and exposures are measured at several different waves, methods applicable to longitudinal datasets are used for statistical analyses. Nested case-control and case-cohort approaches are also used. The outcome variables (Y) shall include presence/absence of disease, the onset of disease (time to event), and variables composed based on the responses to the questionnaires, while the explanatory variable (X) shall include the exposures and confounders.

9.1 Variables by Single Measurement

When analysing the relationship between the outcome variable (Y) and the explanatory variable (X) both of which are measured only once, the increased onset rate of the diseases shall be calculated by performing a regression analysis, controlling confounders related to the outcome variable (e.g. presence/absence of onset, duration, time to event, etc.). The examples of outcome variables (Y) measured only once include those collected at the time of delivery (e.g. birth weight, gender, congenital anomalies). The examples of the exposure factors (X) measured only once are chemical substances collected during pregnancy and those contained in umbilical cord blood.

9.2 Variables by Multiple Measurements

When planned analyses include the outcome variables (Y) that are measured at multiple times (e.g., presence/absence of a certain symptom, variables associated with neuropsychiatric development), the participant's intra-individual variation shall be taken into consideration during their analyses. Multiple measurements of an outcome variable enable quantification of the exposure effect at each time point and estimation of the growth curve of study participants for the target variable.

9.3 Multiple measurement of explanatory variable (X)

When planned analyses include the exposure measurements (X) that are measured at multiple times,

the change in exposures and intra-individual measurement errors shall be incorporated in statistical models using for their analysis.

10 Procedure Manuals

The procedures of measurement, analyses, data collection and management, and quality assurance of measurements of outcome and exposure variables are described in separate standard operating procedures (SOPs). The SOPs stipulate the following: Methods for measurement/analysis, methods for data/sample collection, methods for training personnel responsible for data collection, methods for assuring quality of the study, and methods for auditing conducted to ensure compliance with the study protocol. The SOPs also addresses the methods of data coding/input, the methods of identifying coding/input errors, electronic software and hardware used for data management and the methods of handling biospecimens and environmental samples (i.e., methods of transportation, preservation and disposal). Regional Centres and cooperating health care provide may create their own SOPs for other specific tasks.

11 Publication of the Study Progress and Results

Each Regional Centre periodically reports the progress of the study to the Steering Committee, while the Programme Office updates the storage status of the collected biospecimens and data. The Programme Office then submits an annual study progress report to the MOE each year, which is made available to the public.

The results derived from the study are published in international peer reviewed scientific journals as well as shared with the study participants through JECS website. The detailed methods for publication of the study results are described in a separate SOP.

12 Reporting to the IRB and the Project Evaluation Committee

During the study period, the annual study progress reports are submitted to the Review Committee for Epidemiological Research in the MOE. The Committee reviews the report and provides the Programme Office with feedback from an ethical perspective. Any changes made in the study protocol must be notified to the MOE and reviewed and approved by the Committee.

The annual study progress reports, including change in study protocol and procedure, are also submitted to the Project Evaluation Committee established in the MOE and modified in accordance with their advice/guidance.

13 Research Funding

JECS are funded directly by the MOE. For Adjunct Studies, extramural funding, such as research grants provided by government ministries and agencies (including the MOE) as well as private sectors, is acquired. The principal investigators of the Adjunct Studies are required to promptly report any conflicts of interest generated among the study group members and agencies providing research funds for the Adjunct Study to the Steering Committee.

14 Intellectual Property

JECS allows researchers to apply for a patent for invention produced during the course of the study. The researcher who has produced the invention is required to apply for a patent together with the Principal Investigator of JECS and all the other researchers who have been involved in the invention and belong to the Programme Office, Medical Support Centre or Regional Centres. Rules for patents application based on any materials and biospecimens provided outside to JECS are stipulated elsewhere.

Appendix1: Analytical parameters measured through collection of biospecimen

1. Blood

(1) Exposures

Lead, Cadmium
Total mercury, methyl mercury
Heavy metals
Polychlorinated biphenyl (PCBs): typical isomers 4–7 species
Hydroxylated PCBs: typical isomer
Polybrominated diphenyl ethers (PeBDE, OBDE, etc.)
Dioxins (PCDDs/PCDFs 17 species, Co-PCB (DL-PCB) 12 species)
Hexachlorobenzene (HCB), Pentachlorobenzene (PeCB)
Chlordane analogues (cis-, trans-chlordane, cis-, trans-nonachlor, oxychlordane)
DDT, DDE, etc.
Drin-agricultural chemicals, e.g., dieldrin
Heptachlor analogues (cis-, trans-Heptachlorepoxide)
Hexachlorocyclohexane (α, β, γ, δ-HCH)
Mirex
Chlordecone
Toxaphene
Hexabromocyclododecane (HBCD)
Organic fluorides (PFOA, PFOS, PFCAs (C6, 9-12), PFASs (C6, C10))

(2) Health outcomes

Glycohemoglobin A1c (HbA1c)
Specific IgEs
Total IgE
Red blood cell count, white blood cell count, differential white blood count, haemoglobin, haematocrit, platelet, mean corpuscular volume (MCV), Mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC)
LDL cholesterol
Total cholesterol
Free cholesterol
Triglyceride
HDL cholesterol

Total protein, Albumin
Phospholipid
Folic acid
25(OH) vitamin D
Alkaline phosphatase (ALP)
RLP-cholesterol
Luteinizing hormone (LH)
Follicle-stimulating hormone (FSH)
Oestradiol
Prolactin
Testosterone
Free testosterone
Dehydroepiandrosterone sulfate (DHEA-S)
Androstenedione
Adiponectin
Resistin
Inhibin
Transferrin
Ferritin
Retinol
Tocopherol
Thyroid stimulating hormone (TSH)
Free-thyroxine (Free-T4)
Various specific antibodies
Anti-thyroid peroxidase antibody (TPOAb)
Anti-thyroglobulin antibody (TgAb)
Leptin
Creatinine
C-reactive protein (CRP)

2. Urine

(1) Exposures

Arsenic compounds sorted by chemical form ((III), (V), arsenobetaine, methylarsenic acid, di-methylarsenic acid, trimethyarsine oxide, etc.)
iodine, perchloric acid, nitrate nitrogen, etc.

Organophosphate pesticide metabolites (Dimethyl phosphate (DMP), Diethyl phosphate (DEP), Dimethyl thiophosphate (DMTP), Diethylthiophosphate (DETP), etc.)
3-Methyl-4-nitrophenol (Fenitrothion metabolite), Para-nitrophenol (Parathion metabolite)
Methamidophos (Acephate metabolite)
Pyrethroid metabolites (Phenoxybenzoic acids (PBA), 2,2-dimethylcyclopropane-1-carboxylic acids (DCCA))
Ethylenethiourea (ETU), etc.
Imidacloprid metabolites (6-Chloronicotinic acid), Acetamiprid metabolites, etc.
Pentachlorophenol (PCP), Chlorophenol compounds (atrazine, bentazon, diuron, bromobutide and debrominated body, Glyphosate)
Flutolanil, Carpropamid, Iprodione, Flusulfamide
Nitro musks (Musk xyene, Musk ketone)
Cyclic musks (HHCB (Galaxolide), AHTN (Tonalide), ADBI (Celestolide), AHMI (Phantolide), DPMI (Cashmeran), ATII (Traseolide))
Phthalate metabolites (8–10 species including mono-(2-ethylhexyl) phthalate)
Bisphenol A, Tetrabromobisphenol A, Bisphenol F, Nonylphenol, etc.
Parabens (methyl-, ethyl-, propyl-, butyl-, benzyl-hydroxybenzoate, etc.)
Triclosan
Benzophenone
DEET (*N*,*N*-diethyl-3-methylbenzamide)
Aromatic hydrocarbons and their degradants/metabolites (1-OH-Pyrene, 1-,2/9-,3-,3-OH-Phenanthrene, etc.)
Cotinine, Thiocyanate
Dichlorobenzene
Plant oestrogen
Caffeine
Pyridine
Acrylamide
Tributoxyethyl phosphate (TBEP), Tributyl phosphate (TBP)
8-Hydroxydeoxyguanosine (8-OHdG), 8-isoprostane

(2) Health outcomes

Creatinine
Specific gravity
N-acetyl-beta-D-glucosaminidase (NAG), β2-microglobulin

3. Breast milk

(1) Exposures

Iodine, perchloric acid, nitrate nitrogen, etc.
Dioxins (PCDDs/PCDFs 17 species, Co-PCBs (DL-PCBs) 12 species)
PCBs: typical isomers 4–7 species
Hydroxylated PCBs: typical isomer
Hexachlorobenzene (HCB), Pentachlorobenzene (PeCB)
Chlordane analogues (cis-, trans-chlordane, cis-, trans-nonachlor, oxychlordane)
DDT, DDE, etc.
Drin-agricultural chemicals, e.g., dieldrin
Heptachlor analogues (cis-, trans-Heptachlorepoxide)
Hexachlorocyclohexane (α, β, γ, δ-HCH)
Mirex
Chlordecone
Toxaphene
Polybrominated diphenyl ethers (PeBDEs, OBDEs, etc.)
Polybrominated biphenyls (HBBs, PeBBs, etc.)
Phthalate metabolites (8–10 species including mono(2-ethylhexyl) phthalate)

4. Filter paper blood sample

(1) Health outcome

Thyroid stimulating hormone (TSH)

5. Hair

(1) Exposures

Total mercury

Appendix 2. Variables collected at each phase

Timing	**Method**	**Variables**		
		Outcome	**Exposure**	**Other variables**
First pregnancy trimester	Questionnaire filled in by primary care physician			Expected delivery date, height, weight, pregnancy status, pregnancy complication, delivery history, history of infertility treatment
	Prenatal check-up			Height, weight, blood pressure
	Mother-report questionnaire		Diet, occupation, other environmental exposures	Marital status, family member, pregnancy and delivery history, medical history, medication history, DV K6, SF-8, IPAQ Smoking, occupation, diet, drinking
	Maternal blood	Allergen-specific IgE, Total IgE	Chemical substances with longer half-lives	Complete blood count, TP, Alb, Hb_{A1c}, TC, LDL-C, cholesterol, TG, HDL-C, phospholipids
	Maternal urine		Chemical substances with shorter half-lives	Cotinine, thiocyanate, creatinine, specific gravity of urine
	Father-report questionnaire		Diet, occupation, other environmental exposures	Height, weight, medical history, medication history K6, SF-8, AQ10 Smoking, occupation, diet, drinking

	Paternal blood	Total IgE	Chemical substances with longer half-lives	TP, Alb, TC, LDL-C, cholesterol, TG, HDL-C, phospholipids
Sec-ond–third pregnancy trimester	Prenatal check-up			Weight, blood pressure, 50gGCT
	Mother-report questionnaire		Diet, built environment, occupation, other envi-ronmental exposures	K6, SF-8, IPAQ, AQ10 Stressful events, DV Smoking, occupation, built environment Diet, drinking, eating habits, supplement Education, income, social support
	Maternal blood		Metals, chemical sub-stances with longer half-lives	TP, Alb, TC, cholester-ol, TG, phospholipids, folic acid
	Maternal urine		Chemical substances with shorter half-lives	Creatinine, specific gravity of urine
At delivery	Questionnaire filled in by pri-mary care phy-sician	Multiple birth, miscar-riage, stillbirth, physical measurements, sex of child, labour complica-tion, neonatal jaundice, neonatal complication, congenital anomaly		Weight, blood glucose level, mode of delivery (including painless de-livery), information during pregnancy (in-fection, medication, physical/mental disease, nutrition counseling)
	Umbilical cord blood	Total IgE	Metals, chemical sub-stances with longer half-lives	TP, Alb, TC, cholester-ol, TG, phospholipids
Within a few days after birth	Maternal blood		Metals, chemical sub-stances with shorter half-lives	TP, Alb, TC, LDL- C, cholesterol, TG, phos-pholipids
	Dried blood spot	TSH	Chemical substances with longer half-lives	
	Maternal hair		Hg	
Age one	Questionnaire	Puerperium history,		

month	filled in by primary physician	physical measurements, prolonged jaundice, congenital anomaly		
	Questionnaire	Physical symptoms (e.g., fever), child growth, neuropsychiatric development, allergy		Kangaroo care, crying, sleep, Attachment scale, postpartum depression Smoking, Drinking
	Breast milk		Chemical substances with longer half-lives	
	Child hair		Hg	
Age 6 month	Questionnaire	Medical history, growth, neuropsychiatric development, allergy	Food allergen	Family relations, postpartum depression, parents' health status, partner's participation in parenting, lactation, baby food, binding scale, sleep, vaccination
Age 1	Questionnaire	Medical history, growth, neuropsychiatric development, allergy	Food allergen	Occupation, parents' health status, lactation, baby food, crying, sleep, parenting environment, TV/PDA exposure, social relationships, vaccination, health-related events
Age 1.5	Questionnaire	Medical history, growth, neuropsychiatric development, allergy	Food allergen	Occupation, parents' health status, lactation, baby food, crying, sleep, parenting environment, TV/PDA exposure, social relationships, vaccination, health-related events
	Sub-Cohort Study		Indoor/outdoor air quality (VOCs, NOx, SO_2, O_3, PM), house dust	

			(metals, POPs, pesticides, phthalates, …), dwelling observation	
Age 2	Questionnaire	Medical history, growth, neuropsychiatric development, allergy	Food allergen	Occupation, parents' health status, lactation, baby food, crying, sleep, parenting environment, TV/PDA exposure, social relationships, vaccination, health-related events
	Sub-Cohort Study	Neuropsychiatric development test, paediatrician's examination, blood test (IgE, IgG, IgA, TSH, fT4, 25(OH)D)		
Age 2.5	Questionnaire	Medical history, growth, neuropsychiatric development, allergy		Family relations, parents' health status, parenting stress, social bond, TV/PDA exposure, exercise, health-related events
Age 3	Questionnaire	Medical history, growth, neuropsychiatric development, allergy	Indoor chemical exposure, allergen (dust mites, etc.)	Smoking, parents' health status, socio-economic status, oral cavity, skin condition, defecation, urination, sleep, lifestyle, residential environment, parenting environment, TV/PDA exposure, social relationships, health-related events
	Mother–Child Handbook tran-	Height, weight, head circumference, chest		Pregnancy history, vaccination, dental history

	scription	circumference, growth curve, neuropsychiatric development		
	Sub-Cohort Study		Indoor/outdoor air quality (VOCs, NOx, SO_2, O_3, PM), dwelling observation	
Age 3.5	Questionnaire	Growth curve, neuropsychiatric development		Family relations, parents' health status, occupation, parenting stress, parenting attitude, partner's participation in parenting
Age 4	Questionnaire	Medical history, growth, neuropsychiatric development, allergy		Parents' health status, de-lactation, drinking, parenting environment, oral cavity, skin condition, defecation, urination, temperament, TV/PDA exposure, social relationships, health-related events
	Sub-Cohort Study	Neuropsychiatric development test, paediatrician's examination, blood test (IgE, IgG, IgA, TSH, fT4, 25(OH)D)		
Age 4.5–6	Questionnaire	Medical history, growth, neuropsychiatric development, allergy		Parents' health status, drinking, parenting environment, oral cavity, skin condition, defecation, urination, temperament, TV/PDA exposure, social relationships, health-related

				events
Age 7	Questionnaire	Medical history, growth, neuropsychiatric development, allergy, puberty (female), bone fracture		Stress and participation in child-rearing (parents), vaccination (children)
First grade (age 6–7)	Questionnaire	School health examination record (physical measurements), neuropsychiatric development (ADHD-RS)		K6 (parents)
Age 8	Questionnaire	Medical history, growth, neuropsychiatric development, allergy, puberty (female), bone fracture	Chemical exposure, air pollution, noise, exposure factors, allergens	Live-in relatives, drinking and smoking habits, health status (parents) Passive smoking, medication, diet, the use of screen devices and TV, social life (children)
	Sub-Cohort Study	Neuropsychiatric development test, paediatrician's examination, allergy, metabolism and endocrine system, physical activity	VOCs, biomonitoring using blood, urine and deciduous teeth (phthalates, phenols, pesticides, elements)	
Second grade (age 7–8)	Questionnaire	School health examination record (physical measurements), neuropsychiatric development (SRS, sleep)		
	Second-grade examination	Neuropsychiatric development test, metabolism and endocrine system	Biomonitoring using urine (phthalates, phenols, pesticides, elements)	
Age 9	Questionnaire	Medical history, growth, neuropsychiat-		Stress and participation in child-rearing (par-

		ric development, allergy, puberty (female)		ents), vaccination (children)
Third grade (age 8–9)	Questionnaire	School health examination record (physical measurements), neuropsychiatric development (ADHD-RS, SDQ)		Physical measurements (parents)
Age 10	Questionnaire	Medical history, growth, neuropsychiatric development, allergy, puberty (female)	Chemical exposure, air pollution, noise, exposure factors, allergens	Live-in relatives, drinking and smoking habits, health status (parents) Passive smoking, medication, diet, the use of screen devices and TV, social life (children)
	Questionnaire (children)	Depression, anxiety, resilience		
	Sub-Cohort Study	Neuropsychiatric development test, paediatrician's examination, allergy, metabolism and endocrine system, physical activity	VOCs, biomonitoring using blood, urine and deciduous teeth (phthalates, phenols, pesticides, elements)	
Fourth grade (age 9–10)	Questionnaire	School health examination record (physical measurements), neuropsychiatric development (sleep)		Physical measurements and K6 (parents)
Age 11	Questionnaire	Medical history, growth, neuropsychiatric development, allergy, puberty (female)		Stress, health status (parents) Medication, diet (children)
Fifth grade (age 10–11)	Questionnaire	School health examination record (physical measurements), Physi-		Physical measurements (parents)

		cal abilities (school gymnastics record)		
Age 12	Questionnaire	Medical history, growth, neuropsychiatric development, allergy, puberty (female), the use of growth hormones	Chemical exposure, air pollution, noise, exposure factors, allergens	Live-in relatives, drinking and smoking habits, health status (parents) Passive smoking, medication, diet, the use of screen devices and TV, social life (children)
	Questionnaire (children)	Depression, anxiety, resilience		
	Sub-Cohort Study	Neuropsychiatric development test, paediatrician's examination, allergy, metabolism and endocrine system, physical activity	VOCs, biomonitoring using blood, urine and deciduous teeth (phthalates, phenols, pesticides, elements)	
Sixth grade (age 7–8)	Questionnaire	School health examination record (physical measurements), neuropsychiatric development (SDQ, sleep)		Physical measurements (parents)
	Sixth-grade examination	TBD	TBD	TBD

Appendix 3. Instruments

1. High priority outcome measurements (Category A)

	6 m	1.0 y	1.5 y	2.0 y	2.5 y	3.0 y	3.5 y	4.0 y	4.5 y	5.0 y	5.5 y	6.0 y
Congenital anomalies	Med. hist.	Med. hist.		Med. hist. + MRT								Med. hist. + MRT
Neuropsychiatric development	ASQ, sleep	ASQ, sleep	ASQ, sleep	ASQ, epilepsy (med. hist. + MRT)	ASQ, mod. ES-SENCE-Q	ASQ, sleep, epilepsy (med. hist. + MRT)	ASQ, SRS-P	ASQ, epilepsy (med. hist. + MRT)	ASQ, mod. ES-SENCE-Q	ASQ, SRS, SDQ, epilepsy (med. hist. + MRT)		ADHD-RS, sleep, epilepsy (med. hist. + MRT)
Immune system	ISAAC, food allergy, Kawasaki disease (med. hist. + MRT)	ISAAC, food allergy, Kawasaki disease (med. hist. + MRT)	ISAAC, food allergy, Kawasaki disease (med. hist. + MRT)	ISAAC, food allergy, Kawasaki disease (med. hist. + MRT)		ISAAC, food allergy, Kawasaki disease (med. hist. + MRT)		ISAAC, food allergy, Kawasaki disease (med. hist. + MRT)		ISAAC, food allergy, Kawasaki disease (med. hist. + MRT)		ISAAC, food allergy, Kawasaki disease (med. hist. + MRT)
Metabolism/endocrine system	Growth	Growth, med. hist.	Growth, med. hist.	Growth, med. hist., MRT	Growth, med. hist.	Growth, med. hist.	Growth, med. hist.	Growth, med. hist.	Growth	Growth, med. hist.	Growth	Growth, med. hist., MRT, puberty, body

	6 m	1.0 y	1.5 y	2.0 y	2.5 y	3.0 y	3.5 y	4.0 y	4.5 y	5.0 y	5.5 y	6.0 y
												measure-ment
Others (death, cancer, infections, …)	Med. hist., Cancer (MRT)	Med. hist., resident registry, Cancer (MRT)	Med. hist.	Med. hist., resident registry, Cancer (MRT)		Med. hist., resident registry, Cancer (MRT)		Med. hist., resident registry, Cancer (MRT)		Med. hist., resident registry, Cancer (MRT)		Med. hist., resident registry, Cancer (MRT)
Transcriptions						MCH						MCH

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y
Neuropsychiatric de-velopment	Epilepsy	ADHD		ASD, sleep		LD, ADHD, general psychosis syndrome	KID-SCREEN	sleep			Epilepsy
Immune system	Kawasaki disease, Asthma, Atopic dermatitis, Allergic		Kawasaki disease, Asthma, Atopic dermatitis, Allergic		Kawasaki disease, Asthma, Atopic der-matitis, Al-lergic rhini-		Kawasaki disease, Asthma, Atopic dermatitis, Allergic		Kawasaki disease, Asthma, Atopic der-matitis, Al-lergic rhini-		Kawasaki disease, Asthma, Atopic der-matitis, Al-lergic rhini-

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y
	rhinitis, food allergy		rhinitis, food allergy		tis, food allergy		rhinitis, food allergy		tis, food allergy		tis, food allergy
Metabolism/endocrine system	Bone metabolism (fracture)	Height, weight, puberty	Bone metabolism (fracture)	Height, weight, puberty	Bone metabolism (fracture)	Height, weight, puberty	Bone metabolism (fracture)	Height, weight, puberty	Bone metabolism (fracture)	Height, weight, puberty	Growth, obesity, thyroid function, puberty, bone
Others (Death, cancer, infections, …)	Death, cancer, infection		Death, cancer, infection		Death, cancer, infection		Death, cancer, infection		Death, cancer, infection		Death, cancer, infection

Abbreviations: MRT, medical record transcription; ADHD-RS, Attention Deficit Hyperactivity Disorder Rating Scale; ASQ, Ages & Stages Questionnaires; ISAAC, International Study of Asthma and Allergies in Childhood; PSAI, Pre-School Activity Inventory; SRS, Social Responsiveness Scale; SRS-P, Social Responsiveness Scale Preschool version; SDQ, Strengths and Difficulties Questionnaire; MCH, Mother–Child Handbook

2. Questionnaire instruments by outcomes and exposures

	6 m	1.0 y	1.5 y	2.0 y	2.5 y	3.0 y	3.5 y	4.0 y	4.5 y	5.0 y	5.5 y	6.0 y	6 y +
Health outcomes (Category A)													
Congenital anoma-lies	Med. hist.	Med. hist.		Med. hist. + MRT								Med. hist. + MRT	
Neuropsychiatric development													
Epilepsy		Med. hist.		Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT	Med. hist. + MRT
ASD							SRS-P			SRS			
LD													TBD
ADHD										SDQ		ADHD-RS	ADHD-RS at age 9
Developmental milestones	ASQ	ASQ	ASQ	ASQ	ASQ, mod. ESSENCE-Q	ASQ	ASQ	ASQ	ASQ, mod. ESSENCE-Q	ASQ			
Sleep	IHQ	IHQ	IHQ			IHQ			IHQ			IHQ	IHQ
Immune system													
Kawasaki disease	Med. hist. + MRT	Med. hist. + MRT	Med. hist. + MRT	Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT	Med. hist. + MRT
Asthma		ISAAC	ISAAC	ISAAC		ISAAC		ISAAC		ISAAC		ISAAC	ISAAC
Atopic dermatitis	ISAAC	ISAAC	ISAAC	ISAAC		ISAAC		ISAAC		ISAAC		ISAAC	ISAAC

	6 m	1.0 y	1.5 y	2.0 y	2.5 y	3.0 y	3.5 y	4.0 y	4.5 y	5.0 y	5.5 y	6.0 y	6 y +
Allergic rhinitis				ISAAC		ISAAC		ISAAC		ISAAC		ISAAC	ISAAC
Food allergy	IHQ	IHQ	IHQ	IHQ		IHQ		IHQ		IHQ		IHQ	IHQ
Food protein induced enterocolitis		Med. hist.	Med. hist.										
Metabolism/endocrine system													
Obesity	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ, measurement	IHQ, school records
Growth curve	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ, MHC	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ, measurement, MHC	IHQ, school records
Diabetes		Med. hist.										Med. hist.	Med. hist.
Thyroid function		Med. hist.		Med. hist. + MRT		Med. hist.		Med. hist.		Med. hist.		Med. hist. + MRT	Med. hist.
Puberty		Med. hist.		Med. hist. + MRT		Med. hist.		Med. hist.		Med. hist.		Med. hist. + MRT, exam	Med. hist., exam
Other outcomes													
Death		Resident registry		Resident registry		Resident registry		Resident registry		Resident registry		Resident registry	Resident registry

	6 m	1.0 y	1.5 y	2.0 y	2.5 y	3.0 y	3.5 y	4.0 y	4.5 y	5.0 y	5.5 y	6.0 y	6 y +
Cancer	Med. hist. + MRT	Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT		Med. hist. + MRT	Med. hist. + MRT
Infection	Med. hist.	Med. hist.	Med. hist.	Med. hist.		Med. hist.		Med. hist.		Med. hist.		Med. hist.	Med. hist.
Exposure													
Chemicals			IHQ (household chemicals)			IHQ (household chemicals)			IHQ (household chemicals, diet)			IHQ (household chemicals), HBM	IHQ (household chemicals), HBM
Indoor air pollutants			IHQ			IHQ			IHQ			IHQ	IHQ
Air pollutants	Model	Model	IHQ, model	Model	Model	IHQ, model	Model	Model	IHQ, model	Model	Model	IHQ, model	IHQ, model
Noise	Model	Model	IHQ, model	Model	Model	IHQ, model	Model	Model	IHQ, model	Model	Model	IHQ, model	IHQ, model
Other pollutants			IHQ, public data			IHQ, public data			IHQ, public data			IHQ, public data	IHQ, public data
Allergen			IHQ			IHQ			IHQ			IHQ	IHQ
Covariates/confounders													
Parents													
Nationality	IHQ												
Height and weight	IHQ				IHQ				IHQ				IHQ

	6 m	1.0 y	1.5 y	2.0 y	2.5 y	3.0 y	3.5 y	4.0 y	4.5 y	5.0 y	5.5 y	6.0 y	6 y +
Family	IHQ		IHQ		IHQ		IHQ		IHQ		IHQ		IHQ
Marital status	IHQ												
Smoking			IHQ			IHQ			IHQ			IHQ	IHQ
Drinking			IHQ			IHQ			IHQ			IHQ	IHQ
Occupation		IHQ					IHQ				IHQ		IHQ
Health degree	Self-rated		Self-rated		SF-8		Self-rated		Self-rated		SF-8		Self-rated
Anxiety/depression	EPDS	K6						K6					K6
Attachment	Bonding scale	Bonding scale											
Mental stress	IHQ		IHQ		IHQ		IHQ		IHQ		IHQ		IHQ
Household income						IHQ							IHQ
Community support					IHQ								IHQ
Partners' participa-tion in childcare	IHQ			IHQ			IHQ			IHQ			
Childcare		IHQ	PSI	IHQ	PSI	IHQ	PSI	IHQ		PSI		IHQ	PSI at age 7
Children													
Height, weight, head circumference	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ	IHQ
Family	IHQ		IHQ		IHQ		IHQ		IHQ		IHQ		IHQ
Passive smoking			IHQ			IHQ			IHQ			IHQ, HBM	IHQ, HBM
De-lactation	IHQ	IHQ	IHQ	IHQ				IHQ				IHQ	

	6 m	1.0 y	1.5 y	2.0 y	2.5 y	3.0 y	3.5 y	4.0 y	4.5 y	5.0 y	5.5 y	6.0 y	6 y +
Diet	IHQ	IHQ	IHQ	IHQ					FFQ				FFQ
Cry		IHQ											
Sleep	IHQ	IHQ	IHQ			IHQ			IHQ			IHQ	IHQ
Temperament								IHQ					
Vision/hearing									IHQ				School record
Oral/skin condition	IHQ		IHQ	IHQ		IHQ		IHQ		IHQ		IHQ	School record
Defecation/urination						IHQ, ROME-III		IHQ, ROME-III		IHQ, ROME-III		IHQ, ROME-III	IHQ, ROME-III
Built environment			IHQ			IHQ			IHQ			IHQ	IHQ
Childcare environ-ment		IHQ		IHQ		IHQ		IHQ		IHQ		IHQ	IHQ
TV/PDA exposure		IHQ		IHQ	IHQ	IHQ		IHQ		IHQ		IHQ	IHQ
Social life	IHQ	IHQ		IHQ		IHQ		IHQ		IHQ		IHQ	IHQ
Vaccination	IHQ	IHQ		IHQ								IHQ	IHQ
Health related events		IHQ	IHQ	IHQ	IHQ	IHQ		IHQ					
Exercise					IHQ				IHQ				IHQ, School record
Medication													TBD

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y	G6
Neuropsychiatric development												
Epilepsy	IHQ										IHQ	
ASD	IHQ			SRS							IHQ	
LD	IHQ										IHQ	
ADHD	IHQ	ADHD-RS				ADHD-RS					IHQ	
Developmental milestones	IHQ										IHQ	
Intelligence			Intelligence test (main and sub-cohort)				WISC-IV, intelligence test of mothers (TBD) (sub-cohort)				Intelligence test (main and sub-cohort)	
Sleep				IHQ				IHQ				
General psychosis syndrome						SDQ						SDQ
Depression, anxiety							KID-SCREEN				DSRS, SCAS (TBD)	
Immune system												
Kawasaki disease	IHQ		IHQ		IHQ		IHQ		IHQ		IHQ	
Asthma	ISAAC, IHQ		ISAAC, IHQ FeNO, Spi-		ISAA		ISAAC, IHQ		ISAAC, IHQ		ISAAC, IHQ	

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y	G6
			rometry (sub-cohort)		C, IHQ		FeNO, Spirometry (sub-cohort)				FeNO, Spirometry (sub-cohort)	
Atopic dermatitis	ISAAC, IHQ		ISAAC, POEM, IHQ UK Working Party's skin examination (sub-cohort)		ISAAC, POEM, IHQ		ISAAC, POEM, IHQ UK Working Party's skin examination (sub-cohort)		ISAAC, POEM, IHQ		ISAAC, POEM, IHQ UK Working Party's skin examination (sub-cohort)	
Allergic rhinitis	ISAAC, IHQ		ISAAC, IHQ		ISAAC, IHQ		ISAAC, IHQ		ISAAC, IHQ		ISAAC, IHQ	
Food allergy/FDEIA	IHQ		IHQ		IHQ		IHQ		IHQ		IHQ	
Inflammatory Bowel Disease	IHQ										IHQ	
Immune system	IHQ		Blood test (IgE, IgA, IgG1, IgG4, Measles anti-				Blood test (IgE, IgA, IgG1, IgG4, Measles				Blood test (IgE, IgA, IgG1, IgG4, Measles	

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y	G6
			body) (sub-cohort)				antibody) (sub-cohort)				antibody) (main, sub-cohort)	
Metabolism/endocrine system												
Growth	Pituitary grand disease history	Physical measure-ment rec-ord tran-scription	Height, arm span Blood test (IGF-1) (sub-cohort) Height (main)	Physical measure-ment record transcrip-tion		Physical measure-ment rec-ord tran-scription	Height, arm span Blood test (IGF-1) (sub-cohort)	Physical measure-ment rec-ord tran-scription		Physical measure-ment rec-ord tran-scription	Height, arm span Blood test (IGF-1) (sub-cohort) Height (main)	Physical measure-ment record transcrip-tion
Obesity (DM)	IHQ	Physical measure-ment rec-ord tran-scription	Weight, body composition, waist circum-ference Blood test (HbA1c) (sub-cohort)	Physical measure-ment record transcrip-tion		Physical measure-ment rec-ord tran-scription	Weight, body com-position, waist cir-cumference Blood test (HbA1c) (sub-cohort)	Physical measure-ment rec-ord tran-scription		Physical measure-ment rec-ord tran-scription	IHQ Weight, body com-position, waist cir-cumference Blood test (blood glu-cose, insu-lin) (TBD) (sub-cohort)	Physical measure-ment record transcrip-tion

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y	G6
Thyroid function	IHQ										IHQ Blood test (thyroid hormones, anti-thyroid antibodies, ultrasound) (TBD) (sub-cohort)	
Puberty	IHQ		IHQ Blood test (sex hormones) (sub-cohort)		IHQ		IHQ Blood test (sex hormones) (sub-cohort)		IHQ		IHQ Physician's examination (TBD) (sub-cohort)	IHQ
Bone metabolism	Bone fracture, Vitamin D deficiency		Bone fracture		Bone fracture		Bone fracture		Bone fracture		Bone fracture, Vitamin D deficiency Bone density (TBD) Blood test (25OHD)	Bone fracture, Vitamin D deficiency

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y	G6
											(sub-cohort)	
Other outcomes												
Death	Resident registry		Resident registry		Resident registry		Resident registry		Resident registry		Resident registry	
Cancer	IHQ, registry		IHQ, registry		IHQ, registry		IHQ, registry		IHQ, registry		IHQ, registry	
Infection	IHQ		IHQ		IHQ		IHQ		IHQ		IHQ	
Physical Activity			Wearable device (TBD)				Wearable device (TBD)				Wearable device (TBD)	
Exposure												
Chemicals			IHQ Biomonitoring using blood and urine Personal measurements (VOCs, aldehydes)	Biomonitoring using urine (main)			IHQ Biomonitoring using blood and urine Personal measurements				IHQ Biomonitoring using blood and urine Personal measurements	Biomonitoring using urine (main)

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y	G6
			(sub-cohort)				(VOCs, aldehydes) (sub-cohort)				(VOCs, aldehydes) (sub-cohort)	
Indoor air pollutants			IHQ				IHQ				IHQ	
Air pollutants			IHQ				IHQ				IHQ	
Noise			IHQ				IHQ				IHQ	
Other pollutants			IHQ (exposure factors)				IHQ (exposure factors)				IHQ (exposure factors)	
Others							Indoor bacterial flora (sub-cohort)					
Allergen			IHQ				IHQ				IHQ	
Covariates/confounders												
Parents												
Height and weight						IHQ		IHQ		IHQ		
Family			IHQ				IHQ				IHQ	
Education			IHQ									
Smoking			IHQ				IHQ				IHQ	
Drinking			IHQ				IHQ				IHQ	
Occupation					IHQ						IHQ	
Health degree			IHQ						IHQ			

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y	G6
Anxiety/depression		K6						K6				
Mental stress	IHQ				IHQ				IHQ			
Medical history					IHQ				IHQ			
Household income					IHQ						IHQ	
Community support					IHQ						IHQ	
Partners' participation in childcare	IHQ				IHQ				IHQ			
Children												
Passive smoking			IHQ Biomonitoring using urine (main and sub-cohort)				IHQ				IHQ Biomonitoring using urine (main and sub-cohort)	
Diet			BDHQ15y+JECS, IHQ (dietary behaviour body image)						BDHQ15y+JECS, IHQ (dietary behaviour body image)			

	7y	G1	8y	G2	9y	G3	10y	G4	11y	G5	12y	G6
TV/PDA exposure				IHQ				IHQ				IHQ
Social life			IHQ				IHQ QoL				IHQ QoL	
Vaccination	IHQ										IHQ	
Exercise										IHQ (school record)		
Medication			IHQ (TBD)						IHQ (TBD)			
Resilience								Child questionnaire (TBD)				Child questionnaire (TBD)

Abbreviations: MRT, medical record transcription; ADHD-RS, Attention Deficit Hyperactivity Disorder Rating Scale; ASQ, Ages & Stages Questionnaires; EPDS, Edinburgh Postnatal Depression Scale; ISAAC, International Study of Asthma and Allergies in Childhood; PSAI, Pre-School Activity Inventory; PSI, Parenting Stress Index; SRS, Social Responsiveness Scale; SRS-P, Social Responsiveness Scale Preschool version; SDQ, Strengths and Difficulties Questionnaire; MCH, Mother–Child Handbook; IHQ, in-house developed questionnaire; FFQ, food frequency questionnaire; TBD, to be determined

Japan Environment & Children's Study (JECS)

Sub-Cohort Study Protocol (ver. 2.0)

The Japan Environment and Children's Study Programme Office
National Institute for Environmental Studies

1. Sub-Cohort Study

The Japan Environment and Children's Study (JECS) is a nation-wide birth cohort study which aims to identify environmental factors that affect children's health and development. The main part of JECS (Main Study) aims to recruit 100,000 mother–child pairs and collect data from all the participants. The Main Study utilises questionnaire (including medical record transcription) and modelling for exposure and health outcome measurements. For some exposure and outcome measurements, home visit and person-to-person examination is required. Such include indoor air quality, dust chemistry, neurodevelopmental tests and paediatric examination. Those measurements are particularly expensive so that they cannot be applied to 100,000 participants. Thus, those extended exposure and outcome measurements are performed for a subgroup randomly selected from the Main Study, which is called as the Sub-Cohort Study.

The Sub-Cohort Study is planned to conduct with 5,000 participants who are randomly extracted from all the participants of the Main Study. The participants are recruited from all the Regional Centres. The Sub-Cohort Study employs face-to-face assessment of neuropsychiatric development, body measurement, paediatrician's examination, blood/urine collection for clinical test and chemical analysis, and home visit (ambient air measurement and dust collection).

2. Objectives

The Sub-Cohort Study is designed to collect extended health outcome information and exposure data that are not measured in the Main Study. It employs not only a cross-sectional approach, but also a longitudinal scheme, utilizing unique characteristics of a birth-cohort study. Sub-Cohort Study follows its participants, selected from the Main Study, until the end of the study. This is to examine the onset of diseases as well as change in severity of their symptoms, scores of developmental test and biomarkers, as results of exposure to environmental factors. Additionally, by comparing the results of the Sub-Cohort Study and those of the Main Study in which most of the data are collected through questionnaire, the validity of questionnaires is evaluated.

The outcome variables assessed specifically in the Sub-Cohort Study include following: developmental stage, allergic sensitization, thyroid function, and physical growth. The variables (e.g., Vitamin D) that potentially mediate the association between the environment/diet and child development are also measured in the Sub-Cohort Study.

3. Participants

3.1. Number of participants

The number of participants of the Sub-Cohort Study is planned to be 5,000. This number is determined to enable us to test hypotheses regarding to diseases with a high prevalence (e.g., obesity, allergic disease), with sufficient statistical power.

3.2. Prospective participants

Prospective participants are the participants (children) of the Main Study who were born after 1 April 2013 and were permitted to continuously participate in the Sub-Cohort Study through written consent obtained from their mother or legal guardian. To be a participant of the Sub-Cohort Study, all the following data should be available.

- All the questionnaire data and medical record collected from first trimester to age 6 months
- Biospecimens (except for umbilical cord blood) collected at first trimester, second and third trimester and delivery

3.3. Sampling and recruitment of participants

From the participants of the Main Study meeting the criteria for being a participant of the Sub-Cohort Study, the Programme Office randomly extracts children and creates recruiting lists for each Regional Centre at a regular interval using the data management system and distributes the list to each Regional Centre. The total number of the children on the recruiting list is determined taking account of the proportion of the prospective participants who would agree for participation at each Regional Centre, which is estimated based on the results of recruitment of participants for the Main Study. The number of the children extracted for the list who reside in the study area of each Regional Centre is proportional to the number of the participants of the Main Study in the area. If a Regional Centre has several study areas geographically separated with each other, recruiting lists are created separately for each of the study areas.

Each Regional Centre sends a document including information about the Sub-Cohort Study to the parents of the children on the lists. Then, the Regional Centre calls to the participants' mothers to confirm that they plan to continue to live in the study area until their children reach age 4. Only when the child and his/her parent (or a legal guardian) are considered

to be unlikely to move out of the study area, the parent is provided detailed information and asked to her child's participation in the Sub-Cohort Study. For each child on the recruiting list, the Regional Centre follows this procedure in order, until the number of the children reaches predetermined number. If the number of the children with participation agreement is not sufficient even after all the children on the recruiting list are contacted, the Programme Office repeats the sampling procedure to create an additional recruiting list.

At the initial home visit for environmental measurements (i.e., on the first day of data collection for the Sub-Cohort Study), before the data collection begins, the participant' mother (or legal guardian) is asked to review the information of the Sub-Cohort Study and sign the consent form.

4. Methods

4.1. Overall data-collection schedule

Outcome variables are measured through a developmental test and a medical examination when the participants become ages 2 and 4, while environmental measurements is conducted when they become approximately ages 1.5 and 3. Environmental measurements at ages 1.5 and 3 are completed before measurement of outcome variables at ages 2 and 4, respectively. Participants' urine samples are collected at the timing when outcome variables are measured at ages 4, 6, 8, 10 and 12.

After age 6, we collect health outcome information at the ages of 6, 8, 10 and 12 years. The environmental exposure data will be collected once or twice after 8 years of age. The protocol will be determined in accordance to the Main Study protocols, priority of outcome and exposure measurements and budget. The protocol should be finally approved by the Steering Committee and then by the Institutional Review Boards (IRBs). When changes to the protocol will be made, approval from the IRBs will be obtained and necessary procedures will be taken.

4.2. Measurement of outcome variables

4.2.1. Developmental test

To assess outcome variables in the neuropsychiatric development domain, developmental/cognitive tests are administered individually to the participants (Table 1). For the developmental test used at age 2 and 4, Kyoto Scale of Psychological Development is used, as it

has been most widely used in clinical settings in Japan. The personnel who carry out this test is trained and certificated by the Programme Office.

No test will be performed at the age 6. At age 8, cognitive functions are evaluated using a combination of computer assisted tests (CAT) including the Continuous Performance Test, Mental Number Line, Dimensional Change Card Sorting Test and Finger Tapping Test. After age 10, appropriate examinations will be determined.

Table 1 Developmental tests in the Sub-Cohort Study

	2 y	4 y	6 y	8 y	10 y	12 y
Kyoto Scale of Psychological Development	X	X				
WISC-IV					(TBD)	
CAT (Continuous Performance Test, Mental Number Line, Dimensional Change Card Sorting Test, Finger Tapping Test)				X		TBD

4.2.2. Medical examination

Medical examinations are conducted by paediatricians (Table 2). The medical examinations consist of measurement of height, weight, body composition (at age 6), pulse (at age 2), respiratory rate (at age 2), blood pressure and body temperature; visual examination of head and neck, chest, abdomen, back, and skin (using UK Working Party criteria); neuromotor developmental test and phlebotomy (at ages 2 and 4). It is planned to conduct nitric oxide measurement in children's breath and spirometry at 8 years of age.

Table 2 Medical examination in the Sub-Cohort Study

	2 y	4 y	6 y	8 y	10 y	12 y
Height, weight, waist circumference	X	X	X	X	TBD	TBD
Abdominal circumference			X	X	TBD	TBD

Body composition			X	X	TBD	TBD
Vital sign (pulse, respiratory rate)	X	X				
Blood pressure	X	X	X	X	TBD	TBD
Arm span			X			TBD
Skin examination (UK Working Party criteria)	X	X	X	X	TBD	TBD
Exhaled NO, spirometry				X	TBD	TBD
Neuromotor developmental test	X	X				
Puberty					TBD	TBD
Microbiome					TBD	
CAT (Continuous Performance Test, Mental Number Line, Dimensional Change Card Sorting Test, Finger Tapping Test)			X	X	TBD	TBD

For the phlebotomy, a specific procedure is adopted in order to minimise children's and their parents/guardians' physical pain and mental distress. Local anaesthetic is used if parents/guardians permit it. Parents/guardians are asked to stay in the room throughout the medical examination when they agree. In addition to the paediatrician, co-medical support members stay in the room during the phlebotomy to distract the children to reduce their fear and anxiety. Paediatricians and co-medical staff receive a specific training to provide care for the children before/during/after the blood drawing. The total amount of blood collected from 2 and 4 years old is 4 ml. At the ages of 6, 8, 10 and 12, 10 ml of blood will be collected.

The variables specifically measured through medical are described in the following sections ().

1) Immune system disorders/allergy

   Nonspecific IgE, specific IgE, IgG, IgA of inhalant and food antigens (10 items)

2) Metabolism/endocrine system

   Thyroid stimulating hormone (TSH), free thyroxine (fT4), 25(OH) Vitamin D, T4, T3, fT3, IGF-1, LH, FSH, E2, testosterone, DHEA-S, HbA1c, glucose, insulin, LDL, HDL, TG.

3) Biomonitoring (persistent organic pollutants, etc.)

Table 3 Blood tests and biomonitoring items in the Sub-Cohort Study

	2 y	4 y	6 y	8 y	10 y	12 y
Non-specific IgE	X	X	X	X	TBD	TBD
Specific IgE, IgA, IgG1 and IgG4	X	X	X	X	TBD	TBD
Measles antibody				X		
TSH, fT4	X	X	X	X	TBD	TBD
T4, T3, fT3				X	TBD	TBD
25(OH)Vitamin D	X	X	X	X	TBD	TBD
IGF-1			X	X	TBD	TBD
LH, FSH, steroid hormones			X	X	TBD	TBD
HbA1c, glucose, insulin, LDL, HDL, TG						TBD
Chemical substances	X	X	X	X	X	X

4.3. Evaluation of environmental exposure at ages 1.5 and 3 years

Children's environmental exposures are measured the ambient environmental measurements and biomonitoring. Environmental measurements include indoor and outdoor volatile organic compounds (VOCs) by passive diffusion samplers, particulate matter by gravimetric determination and house dust collection. Dwelling observation is also conducted to observe possible environmental hazards inside and around the children's home. Those are all performed by trained and certificated field staff of each Regional Centre. Biospecimens collected during the medical examination are tested for clinical biochemistry and aliquoted into cryovials for later chemical analysis.

4.3.1. Mite allergen/Endotoxin

Mites and endotoxin are measured in dust collected from the mattress/futon that children regularly use for sleep. The field staff vacuum a specific area (50 cm x 1 m) of the children's

mattress/futon using a specified handy-cleaner with a designated filter for 2 minutes.

4.3.2. Heavy metals/non-volatile organic compounds

Heavy metals (e.g., lead, cadmium) and organic compounds (e.g., PCBs, PBDEs, agricultural chemicals, phthalates) are measured in house dust in vacuum cleaner bags. Participants are asked to install the specified vacuum cleaner bag and collect dust in their usual manners for a month. Those who use vacuum cleaners without bags (e.g., cyclonic vacuum cleaners) are asked to collect dust for one month and transfer the dust into plastic bags provided by the field staff. Priority chemicals are measured in biospecimens.

4.3.3. Volatile organic compounds

Volatile organic compounds (VOCs) are sampled by passive diffusion samplers and analysed by gas chromatography or liquid chromatography mass spectrometer. VOCs measured include formaldehyde, acetaldehyde, toluene, ethylbenzene, xylene, styrene, and *p*-dichlorobenzene. Nitrogen oxides (NOx), and sulphur oxides (SOx) are also measured. Samplers are installed in the room in which children spends most of the time. The samplers are also placed outside the house. VOCs are determined as average concentrations of seven days.

4.3.4. Particulate matters

Particulate matters (PMs) are collected by an active pump operated intermittently for seven days (5 min pumping and 30 min resting). PMs are collected in the same places where volatile organic compounds are collected (both indoor and outdoor). $PM_{2.5}$ and PM_{10} are measured separately by a gravimetric method.

4.3.5. Dwelling observation

Room temperature and humidity are recorded during the VOC sampling. The field staff conduct observations using the dwelling observation sheet. They also fill the sheet collecting the information about commodity (e.g., insecticide and air fresheners) and the type and amount of chemical substances of daily use.

4.4. Evaluation of environmental exposure after age 6

Chemical substances to which children are being exposed on daily bases may have relatively short biological half-lives. Since those compounds or their metabolites are often detected in urine, urine samples are collected from children at the ages of 6, 8, 10 and 12 and subject to biomonitoring. Blood samples will be analysed for persistent organic pollutants, chemicals with relatively long biological half-lives, toxic elements and essential elements.

4.4.1. Personal monitoring

Methodology using passive samplers or a gas sensor for personal monitoring of VOCs and aldehydes is being developed. Appropriate modifications will be made according to the results of the method development.

4.4.2. Personal monitoring

A geographic noise model is constructed to estimate environmental noise that each participant is exposed to. In order to assess average sound insulation of participants' houses, noise levels are measured inside and outside of the selected participants' houses which are likely to be exposed to traffic, railroad and/or aircraft noises. The houses and timing of measurements are determined by the noise model.

5. Reporting results to the participants

All the collected individual data including results of developmental tests, medical examinations, biomonitoring and environmental measurements are reported to the corresponded participant. The results are not reported to individuals who refuse to receive the data. Special teams are organised within the Programme Office, Medical Support Centre and each Regional Centre to answer questions from the participants who have received the report.

Japan Environment and Children's Study
International Advisory Board Meeting
On 2 and 3 September 2019

Ohyama Memorial Hall
National Institute for Environmental Studies, Tsukuba, Japan

ADVISORS

Linda Birnbaum (Chair)

PhD, DABT, ATS Director
National Institute of Environmental Health Sciences and National Toxicology Program

Linda S. Birnbaum, Ph.D., is director of the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, and the National Toxicology Program (NTP). A board-certified toxicologist, Birnbaum has served as a federal scientist for nearly 39 years. Prior to her appointment as NIEHS and NTP Director in 2009, she spent 19 years at the U.S. Environmental Protection Agency (EPA), where she directed the largest division focusing on environmental health research.

Birnbaum has received many awards and recognitions. In 2016, she was awarded the North Carolina Award in Science. She was elected to the Institute of Medicine of the National Academies, one of the highest honors in the fields of medicine and health. She was also elected to the Collegium Ramazzini, an independent, international academy comprised of internationally renowned experts in the fields of occupational and environmental health and received an honorary Doctor of Science from the University of Rochester and a Distinguished Alumna Award from the University of Illinois. She also received an Honorary Doctorate from Ben-Gurion University, Israel; the Surgeon General's Medallion 2014; and 14 Scientific and Technological Achievement Awards, which reflect the recommendations of EPA's external Science Advisory Board, for specific publications.

Birnbaum is an active member of the scientific community. She was vice president of the International Union of Toxicology, the umbrella organization for toxicology societies in more than 50 countries, and former president of the Society of Toxicology, the largest professional organization of toxicologists in the world. She is the author of more than 800 peer-reviewed publications, book chapters, and reports. Birnbaum's own research focuses on the pharmacokinetic behavior of environmental chemicals, mechanisms of action of toxicants including endocrine disruption, and linking of real-world exposures to health effects. She is also an adjunct professor in the Gillings School of Global Public Health, the Curriculum in Toxicology, and the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill, as well as in the Integrated Toxicology and Environmental Health Program at Duke University.

A native of New Jersey, Birnbaum received her M.S. and Ph.D. in microbiology from the University of Illinois at Urbana-Champaign.

Åke Bergman

PhD, Professor
Department of Environmental Science and Analytical Chemistry (ACES)
Stockholm University

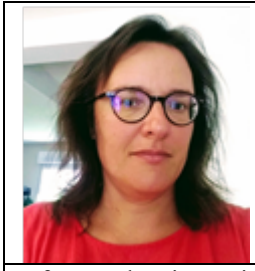
Åke Bergman served as professor in Environmental Chemistry at Stockholm University since 1993 and Guest professor at Tongji University in Shanghai from 2012, and nowadays also professor at Orebro University (Sweden). He was director of the research center, Swetox for the past five years and now leading the establishment of the Swedish Academic Consortium on Chemical Safety (Swaccs). Bergman has a broad interdisciplinary approach in his research with particular focus on organic environmental chemistry and with emphasis on persistent organic pollutants and related compounds. He has worked with chemical synthesis, chemical reactivity, chemical analysis, kinetics of pollutants, e.g. of PCBs, DDTs, brominated flame retardants and chlorinated paraffins (CPs). Bergman has a long-lasting interest in research on endocrine disrupting chemicals (EDCs). He has served at numerous national and international expert groups and review panels. He was the coordinator of the UNEP/WHO program panel for the state of the science of endocrine disruption 2012. Bergman has published around 500 scientific articles and numerous outreaching activities.

Michael Borghese, PhD
Targeted Epidemiology & Biomonitoring Section
Population Studies Division
Environmental Health Science and Research Bureau
Environmental and Radiation Health Sciences Directorate
Healthy Environments and Consumer Safety Branch
Health Canada

Michael is an Epidemiologist with the Environmental Health Science and Research Bureau at Health Canada. His group is responsible for conducting and managing scientific studies on targeted epidemiology and biomonitoring of environmental chemicals. Michael primarily conducts research on the Maternal-Infant Research on Environmental Chemicals (MIREC) Research Platform, which is one of Canada's chemical biomonitoring initiatives supported under Canada's Chemicals Management Plan. His research investigates:

- The effects of prenatal exposure to environmental chemicals on the health of pregnant women, infants, and children
- Biomonitoring and surveillance efforts for legacy and emerging environmental chemicals
- The effects of lifestyle behaviours (e.g., physical activity, sedentary behaviour, and sleep, diet, stress, substance use) in the health of pregnant women, infants, and children

Michael has a broad background in Epidemiology, Statistics, Physiology, Health/Life sciences and Kinesiology.



Ghislaine Bouvier
Associate Professor
Bordeaux Population Health Center INSERM U1219
Bordeaux University

After a PhD in Paris dealing with pesticide exposure assessment in the general population, I work in Bordeaux in the team of the Professor Isabelle Baldi, Work Health Physician and epidemiologist.
I am responsible of research programs dealing with domestic or occupational exposure to pesticides of the population, and we also recently developed studies on the topic of residential exposure to pesticides due to geographical proximity of agricultural areas. We try to develop new tools or to improve existing tools to better characterize exposure of the populations and are very interested in Exposure Assessment Sciences.
We also study potential health effects linked to these exposures to pesticides, such as cancers and especially brain tumors, blood cancers and sarcoma, neurologic disorders, and respiratory and reproductive outcomes.
As a more recent development, we conduct studies on electric and magnetic field exposures (ELF and RF) in general population and we collaborate with worldwide teams involved in this topic in order to develop or improve tools such as Job Exposure Matrices.
I am member of the advisory board of the Elfe study and coordinator of the Physical Agent Research Group, gathering researchers working on UV, Ionizing and non-Ionizing Radiations, and member of the Chemical Agent Research Group. In the Elfe cohort, we studied the link between occupational ELF exposure of mothers and SGA and prematurity, and we will soon be able to study this regarding RF occupational exposure. We contributed to the Popeye project, where we worked on occupational exposure to pesticides and birth outcomes. We plan to further study the link between these exposures and other outcomes such as child development, in collaboration with researchers involved in this topic.
As a teacher, I was in charge of a Bachelor degree in Nutrition and Health, and I am now co-supervisor with Isabelle Baldi of the Master “Occupational and Environmental Health”, part of the Public Health Master Degree proposed by the ISPED Department of the University of Bordeaux (Institute of Public Health and Development). I also teach in Medicine and Pharmacy Colleges (epidemiology, public health, chemical and physical agents of the environment and their health impacts, hydrology, …).
I am president of the Scientific Committee of the “Residential Proximity to agricultural lands, Exposure and Health” program, conducted by the French National Agency For Public Health (Santé Publique France) and the French Agency for Food, Environmental and Occupational Health & Safety (Anses).
I am the co-author of 30 scientific publications indexed in the PubMed database and of 15 oral and poster presentations in international congresses.

Kim Suejin
Director
Humidifier Disinfectant Health Center
National Institute of Environment Research (NIER)
Ministry of Environment

Suejin KIM is a senior researcher of the National Institute of Environmental Research (NIER), Ministry of Environment (MOE) of Republic of Korea. She joined the NIER in 1995 and has been conducted research about exposure assessments for hazardous chemicals, indoor air pollution and related policies.
In 2014, she moved to Environmental Health Research Division and planned and conducted human bio-monitoring program of the Korean, KoNEHS project (the Korean National Environmental and Health Survey). And, from Jun. 2015 to Mar. 2019, she is conducting a National Birth Cohort Study (Ko-CHENS; Korean CHildren’s ENvironmental and health Study) to identify the effects of environmentally

hazardous chemicals on the health of pregnant women and children, also is constructing a bio-bank for long-term storage of biological samples such as blood, cord blood and urine.
Currently, she is the director of HDHC (Humidifier Disinfectant Health Center) and is conducting research to identify the causes of health effects from humidifier disinfectants. And is also promoting long-term follow-up health monitoring for victims. Humidifier disinfectant damage is one of the largest environmental health incidents in Korea.

Marike Kolossa-Gehring
Head
Section II 1.2 Toxicology
German Environment Agency

Dr. Marike Kolossa-Gehring is biologist and toxicologist and got her PhD from the Christian-Albrechts-University Kiel, Germany. Her research focusses on toxicology and human biomonitoring (HBM). She is Head of Section "Toxicology, Health-related Environmental Monitoring" at the German Environment Agency (UBA) and coordinator of the European Joint Programme HBM4EU, a joint effort of more than 110 partners from 28 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. At the UBA she is in charge of managing the German Federal Human Biomonitoring Program consisting of German Environmental Survey (GerES), the Human part of the German Environmental Specimen Bank (ESB), the German Human Biomonitoring Commission, and the HBM cooperation between the German Chemical Industry Association (VCI) and the Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety (BMU).
She was involved in the development of assessment strategies and guidelines at the national, EU and OECD level and vice-chair and chair of the OECD Endocrine Disruptor Testing and Assessment Task Force from 2006 to 2010. She was Work Package Leader in the EU HBM projects ESBIO, DEMOCOPHES and COPHES, the Consortium to Perform Human Biomonitoring on a European Scale preparing and piloting a European human biomonitoring study. From 2011 to 2014 she was Governmental Councillor of the International Society of Exposure Science (ISES). She has authored and co-authored more than 100 peer reviewed papers, 10 book chapters and a various scientific reports.

Per Magnus
Centre Director
Centre for Fertility and Health
Norwegian Institute of Public Health

Per Magnus graduated from the Medical School at the University of Oslo in Norway in 1976. After internship in surgery, internal medicine and general practice as well as military service he became a specialist in medical genetics in 1985. In the same year he defended his PhD thesis on the causes of variation in birth weight. Since 1985, he is a general epidemiologist at the Norwegian Institute of Public Health in Oslo, and since 1996, adjunct professor at the University of Oslo. Main topics have been perinatal outcomes, asthma and allergies, HIV/AIDS, environmental hazards, cardiovascular diseases, genetics as well as neurodevelopmental disorders. He has participated in the conduct of a series of cohort and case-control studies. Since 1998, he has been the principal investigator of the Norwegian Mother, Father and Child Cohort Study (MoBa), and since 2017 the director of the Centre of Fertility and Health, set up through the Norwegian Research Council's Centres of Excellence funding scheme. He has published about 440 papers in peer-reviewed scientific journals.

Sjurdur F. Olsen
PhD, Professor
STATENS SERUM INSTITUT

Sjurdur F Olsen and colleagues have published >200 peer reviewed articles mainly within the field of pregnancy nutrition and health. He and colleagues were the first to suggest, and show, in two papers in The Lancet that fish oil in pregnancy could delay spontaneous delivery and reduce preterm risk, a contention since corroborated in trials by others and a recent Cochrane Review. SF Olsen has since 1994 been part of the team that established the Danish National Birth Cohort (DNBC). He is member of DNBC's Scientific Management Team and has been responsible for the introduction, financing, implementation, and conduct of the maternal dietary component of DNBC; from 1996-2003, 70,000 pregnant women completed a comprehensive FFQ, generating the first large prospective database on pregnancy diet of its kind worldwide. Dr. Olsen has served on several expert committees. While he was a member of the Danish Nutrition Council, he chaired the Council's expert panel that published an extensive report reviewing the scientific evidence underpinning dietary advice in relation to pregnancy, and he was member of the expert group on 'Pregnancy and Lactation' for updating the 5th version of the Nordic Nutrition Recommendations financed by The Nordic Council of Ministers. For six years, he served as member of the Scientific Advisory Committee of the Nutricia Research Foundation. Dr. Olsen is involved in several international collaborative efforts. In a European context, Olsen was partner in the Framework Programme (FP) 5 project NUTRIX and Theme Leader in the FP6 Integrated Project, EARNEST; and he was partner in the Early Nutrition Project, another Large-Scale Integrated Project funded by EU, under FP7. He was Danish co-PI of the NIH/NICHD initiated the Diabetes and Women's Health-study, which is seeking to identify determinants (medical, lifestyle, genetic) and their interactions for the progression from gestational diabetes to type 2 diabetes. Together with Professor Zhou from the Shanghai Institute of Planned Parenthood Research he initiated and is co-PI on a large RCT with fish oil in the Gan su and Xian si Provinces of China, investigating the effects of fish oil supplementation in pregnant women. Sjurdur F Olsen is Chief Physician at Statens Serum Institut, Copenhagen; Professor in Epidemiology with Special Focus on Fetal Programming at University of Copenhagen; and Adjunct Professor in Nutrition, Harvard School of Public Health. Until recently, Olsen was Centre-Leader of the Danish Center for Fetal Programming, a multidisciplinary research consortium funded by Innovation Fund Denmark. Recent examples of interdisciplinary 'cross-fertilization' research deriving from the Centre, include papers on 'gluten and offspring T1D' (undertaken as a collaboration between epidemiologists and researchers doing animal experiments) and 'protein and offspring metabolic health' (a collaboration between epidemiologists and researchers doing clinical physiology). Olsen and team organized, in 2013 and 2014, two international symposia on 'Fetal Programming', both of which took place in Novo Nordic Foundation's Auditorium in Copenhagen, and with >100 participants each time.

Song Sanghwan
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Experience
April 2019–Present
Senior Researcher: Korea Children Environmental Study (Ko-CHENS) Core center, Environmental Health Research Division, National Institute of Environmental Research
2017–2018

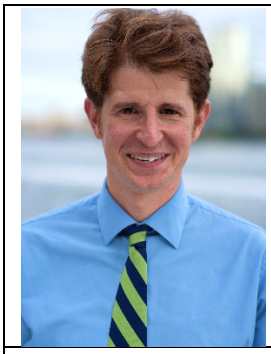
Senior Researcher: Environment Epidemiology Investigation T/F,, Environmental Health Research Division, National Institute of Environmental Research
- Investigation of environmental exposures and their health effects in residents near pollutants sources (industrial area, abandoned mine, chemical accident, etc.)

2007~2014

Researcher: Environmental Health Research Division, National Institute of Environmental Research
- Study on the health effects of Exposure to Asian sand dust and (ultra) fine particulates in children.
- Investigation of exposure to Mercury and its Health effects in elementary school children

Education

Degree	Institution	year conferred
Master of Public Health (Environmental Health)	Seoul National University Seoul, S. Korea	1998
Doctor of Public Health (Environmental Health)	Seoul National University Seoul, S. Korea	2012



Leonardo Trasande, MD, MPP

Professor, Department of Pediatrics
Chief, Division of Environmental Pediatrics
Professor of Environmental Medicine & Population Health
NYU School of Medicine

Leonardo Trasande, MD, MPP is an internationally renowned leader in children's environmental health. His research focuses on identifying the role of environmental exposures in childhood obesity and cardiovascular risks, and documenting the economic costs for policy makers of failing to prevent diseases of environmental origin in children proactively. He also holds appointments in the Wagner School of Public Service and NYU's College of Global Public Health. He is perhaps best known for a series of studies published in Lancet Diabetes and Endocrinology and the Journal of Clinical Endocrinology and Metabolism that document disease costs due to endocrine disrupting chemicals in the US and Europe of $340 billion and €163 billion annually, respectively. Dr. Trasande leads one of 35 centers across the country as part of the National Institute of Health's Environmental Influences on Child Health Outcomes program.

LIST OF PARTICIPANTS

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Japan Environment and Children's Study		
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Shoji Nakayama	Programme Office	Deputy Director
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Hiroaki Shibuya	Programme Office	Deputy Manager
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Miho Nakada	Programme Office	Specialist
Miki Ebisawa	Programme Office	Specialist
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