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ABSTRACT

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Tohoku Study of Child Development and Exposure Assessment

Nippon Eiseigaku Zasshi, 64, 749–758 (2009)
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Dioxins, polychlorinated biphenyls (PCBs), and organochlorine pesticides are bioaccumulative chemicals that are considered to be toxic contaminants. These chemicals are classified as persistent organic pollutants (POPs). We have started a prospective cohort study to examine the effects of perinatal exposure to these chemicals as well as methylmercury on neurobehavioral development in Japanese children. In this article, the method and the consequence of exposure assessment were described. The concentrations of POPs in maternal blood, cord blood, and breast milk were determined by high-resolution gas chromatography–high-resolution mass spectrometry. In breast milk samples, *p,p′*-DDE was the predominant pollutant, total PCB and *β*-HCH being the other major constituents. Mirex and major toxaphenes were also detected in all samples even though these chemicals have never been used in Japan. Simple correlation analysis showed high correlations among the three sample materials, indicating that there was a high degree of consistency of chemicals in the body. Major chemicals were also intercorrelated with other chemicals in either of the three sample materials. These findings indicate the presence of coexposure to multiple POPs. Multiple regression analysis indicated that the concentrations of PCBs were affected by the age of mother, parity, and maternal fish intake. These results are informative in terms of considering the strategy to reduce the body burden of POPs in females. The chemical analysis were performed by two different institutes. Multiple regression analysis also showed that the result of chemical analysis was affected significantly by the difference in analyzing institute. This finding suggest the importance of consistency in chemical analysis and the necessity for quality and accuracy control using reference materials.

Adverse Birth Outcomes of Maternal Smoking During Pregnancy and Genetic Polymorphisms: Exploiting Gene–Environment Interaction

Nippon Eiseigaku Zasshi, 64, 759–764 (2009)
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It has been recognized that metabolic enzymes mediating genetic susceptibility to environmental chemicals such as polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans and polychlorinated biphenyls might be related to adverse human health. Recent studies, including the Hokkaido Study of Environmental and Children's Health, have shown that metabolic enzymes mediating genetic susceptibility to environmental chemicals including tobacco smoke might be related to adverse birth outcomes. Certain maternal genetic polymorphisms in the polycyclic aromatic hydrocarbons (PAHs)-metabolizing enzymes have been shown to enhance the association between maternal smoking and infant birth weight in both Caucasians and Japanese. For maternal genetic polymorphisms encoding the *N*-nitrosamine-metabolizing enzymes, we found that infant birth weight, birth length and birth head circumference were significantly smaller among infants of smokers than among those of nonsmokers and quitters. The adverse effects of maternal smoking on infant birth size may be modified by maternal genetic polymorphisms. Further study is required to clarify the potential association between genetic polymorphisms and cognitive function in childhood, because it has been reported that a small birth length or a small head circumference at birth might affect neurobehavioral development during early childhood. It is necessary to elucidate additive impacts of genetic factors on adverse effects of various chemicals commonly encountered in our daily lives, follow up the development of children, and carry out longitudinal observation.

Profiling Prospective Birth Cohort Studies on Relationship between Environment and Children's Health: Various Issues and Aspects Involved in Evaluating Development in Children

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Polychlorinated biphenyls (PCBs) and dioxins are persistent environmental pollutants. The effects of these pollutants on neurodevelopment in children have been assessed in longitudinal studies performed in areas with low-level contamination of PCBs and dioxins. Some of these studies have shown that the PCBs and dioxins induced adverse effects on the neurodevelopment of children. However, other studies did not reveal any negative effects of these chemicals on development. Thus, consistent results describing the effects of low-level PCB and dioxin exposure on children's development have not been obtained. To study the effects of these agents on the neurodevelopment of children, it is essential to identify the target of the study, determine the duration of the study, and devise a protocol for performing the studies, as these are important factors that affect research findings. Furthermore, detailed evaluations of neurodevelopment should be performed by longitudinal methods to obtain reliable measurements of outcomes. However, it is necessary to assess the burden on subjects; this step can help reduce the loss of subjects and determine the most suitable approach to evaluating neurodevelopment.

Profile and Issues of Prospective Birth Cohort in Japan: The Hokkaido Study of Environment and Children's Health

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Recently, the effects of environmental risk factors including chemical compounds and parents' lifestyles on the health of the next generations have widely gathered public concerns around the world because of the vulnerability of children to such environmental risk factors. To elucidate the processes and mechanisms of the effects in more detail, the authors started a prospective birth cohort study, namely, the Hokkaido study of Environment and Children's Health in Hokkaido, the northern area of Japan. The study consists of two cohorts: a large-scale cohort throughout Hokkaido and a hospital-based small-scale cohort. The former was established in 2003 in collaboration with forty obstetric hospitals and clinics around Hokkaido to estimate the prevalence of congenital malformations and investigate the association of congenital anomalies with environmental risk factors in pregnant mothers at a background level. The latter was lunched in 2002 at the time of enrollment of pregnant women recruited at an obstetric hospital in Sapporo so as to examine the relationships of environmental substances such as polychlorinated biphenyls (PCBs), dioxins, persistent organic pollutants (POPs), and heavy metals with infants' and children's health outcomes including birth size, neurobehavioral development, thyroid function, and immunologic system. In the study of both cohorts, we attempt to determine the role of gene polymorphism on the occurrence of adverse outcomes in infants and children. Although the prospective cohort study with well-designed epidemiological protocols may provide many scientific lines of evidence, many human and financial resources are required to support the study until its completion and maintain the biobanks as well as data banks. In Japan, it is urgently necessary to establish a system that supports the implementation and management of a cohort study.

Epidemiological Research on Children's Environmental Health: Clarification of Environmental Risks that Affect Children's Development

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In accordance with the Declaration of the Environment Leaders of the Eight on Children's Environmental Health (Miami Declaration) in 1997, the Japanese government (the Ministry of Environment, Japan) organized a commission tasked to discuss issues related to the present situation of the environmental health of children (Advisory Commission for Children's Environmental Health). Epidemiological research on children's environmental health has been recommended as one of the priority projects by the commission because the effects of environmental factors on children's health are clarified by only studies using children as subjects, particularly, a birth cohort study, and not by animal experiments. The Advisory Committee of Epidemiological Research on Children's Environmental Health was established in 2007 and decided to start a nationwide birth cohort study following up children from pregnancy to 12 years old. Under the Advisory Committee, a working group composed of scientific experts, including epidemiologists, toxicologists, obstetricians, orthopedists, and statisticians, was organized in 2008. Pilot studies are going to be conducted in several areas in Japan with the support of the working group. Study hypotheses will also be decided by the working group soon. The full-scale survey will start in 2010.

Causal Inference in Medicine Part I. Counterfactual Models: An Approach to Clarifying Discussions in Research and Applied Public Health

Nippon Eiseigaku Zasshi, 64, 786–795 (2009)
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A central problem in natural science is identifying general laws of cause and effect. Medical science is devoted to revealing causal relationships in humans. The framework for causal inference applied in epidemiology can contribute substantially to clearly specifying and testing causal hypotheses in many other areas of biomedical research. In this article, we review the importance of defining explicit research hypotheses to make valid causal inferences in medical studies. In the counterfactual model, a causal effect is defined as the contrast

between an observed outcome and an outcome that would have been observed in a situation that did not actually happen. The fundamental problem of causal inference should be clear; individual causal effects are not directly observable, and we need to find general causal relationships, using population data. Under an "ideal" randomized trial, the assumption of exchangeability between the exposed and the unexposed groups is met; consequently, population-level causal effects can be estimated. In observational studies, however, there is a greater risk that the assumption of conditional exchangeability may be violated. In summary, in this article, we highlight the following points: (1) individual causal effects cannot be inferred because counterfactual outcomes cannot, by definition, be observed; (2) the distinction between concepts of association and concepts of causation and the basis for the definition of confounding; (3) the importance of elaborating specific research hypotheses in order to evaluate the assumption of conditional exchangeability between the exposed and unexposed groups; (4) the advantages of defining research hypotheses at the population level, including specification of a hypothetical intervention, consistent with the counterfactual model. In addition, we show how understanding the counterfactual model can lay the foundation for correct interpretation of epidemiologic evidence.

Causal Inference in Medicine Part II. Directed Acyclic Graphs: A Useful Method for Confounder Selection, Categorization of Potential Biases, and Hypothesis Specification

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Confounding is frequently a primary concern in epidemiological studies. With the increasing complexity of hypothesized relationships among exposures, outcomes, and covariates, it becomes very difficult to present these hypotheses lucidly and comprehensively. Graphical models are of great benefit in this regard. In this article, we focus on directed acyclic graphs (DAGs), and review their value for confounder selection, categorization of potential biases, and hypothesis specification. We also discuss the importance of considering causal structures before selecting the covariates to be included in a statistical model and the potential biases introduced by inappropriately adjusting statistical models for covariates. DAGs are nonparametric and qualitative tools for visualizing research hypotheses regarding an exposure, an outcome, and covariates. Causal structures represented in DAGs will rarely be perfectly "correct" owing to the uncertainty about the underlying causal relationships. Nevertheless, to the extent that using DAGs forces greater clarity about causal assumptions, we are able to consider key sources of bias and uncertainty when interpreting study results. In summary, in this article, we review the following three points. (1) Although researchers have not adopted a consistent definition of confounders, using DAGs and the rules of d-separation we are able to identify clearly which variables we must condition on or adjust for in order to test a causal hypothesis under a set of causal assumptions. (2) We also show that DAGs should accurately correspond to research hypotheses of interest. To obtain a valid causal interpretation, research hypotheses should be defined explicitly from the perspective of a counterfactual model before drawing DAGs. A proper interpretation of the coefficients of a statistical model for addressing a specific research hypothesis relies on an accurate specification of a causal DAG reflecting the underlying causal structure. Unless DAGs correspond to research hypotheses, we cannot reliably reach proper conclusions testing the research hypotheses. Finally, (3) we have briefly reviewed other approaches to causal inference, and illustrate how these models are connected.

Current Problems Arising from Not Having Biosafety Level 4 Laboratories in Japan: Qualitative Study of Infectious Disease Experts

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Objectives: No public consensus exists yet on handling Biosafety Level 4 agents and no laboratory is operational at BSL4 in Japan. A discussion that includes neighboring residents and experts should be initiated to communicate risks. In this article, we present the current situation and prioritize problems we presently face.
Methods: A three-stage Delphi survey was conducted. The subjects were 22 persons with extensive experience and knowledge of infectious diseases. Seven projections and issues were made with regard to the problems arising from the lack of an operational BSL4 laboratory. These were tabulated by the KJ method. The top seven projections were scored, such that the top received seven points and the last received one point.
Results: A total of 51 projections were obtained for the first part of the survey, 39 for the second, and 29 for the last. The projection with the highest score was that it is impossible to cope with newly emerging infectious diseases. The second was that complete diagnoses are impossible without a BSL4 laboratory. All projections and issues were divided into the following four main groups: issues for researchers and laboratory staff, clinical practice and research on BSL4 agents, domestic and global security, and Japan's international position.
Conclusion: We clarified possible problem arising from not having BSL4 laboratories in Japan. The identification of projections by the Delphi survey in this study should be considered as one of many attempts to develop effective risk communication strategies.

Evaluation of New Saliva Collection Device for Determination of Salivary Cotinine, Cortisol, Dehydroepiandrosterone and Testosterone Concentrations

Nippon Eiseigaku Zasshi, 64, 811–816 (2009)
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Objectives: This study was conducted to examine the effectiveness of a new salivary collection device (ϕ 10 mm × 25 mm) made of polypropylene and polyethylene polymers (Salisoft®).
Methods: Experiment 1. We measured the absorption capacity of the new device by two methods. Next, we examined whether the device affected the pH of 0.1 M $NaHCO_3$ solution (pH 8.7) and 0.1 M

sodium phosphate buffer solution (pH 6.0). Experiment 2. We compared three saliva collection methods: by passive drool, using a cotton device (Salivette®), and using the new device. Saliva samples were collected from 12 men (average age 31.5 ± 17.1 years). Saliva samples were assayed for cotinine, cortisol, dehydroepiandrosterone, and testosterone concentrations by enzyme immunoassay, and the pH of saliva samples were measured.
Results: After this device was put in the mouth for one minute, 1.28 ± 0.13 mL (mean ± SD, $N = 6$) of saliva samples were obtained. The mean pHs of saliva samples collected using Salisoft® and by passive drool did not differ significantly, whereas that of saliva samples collected with Salivette® was significantly low. Saliva samples collected with Salisoft® and those obtained by passive drool did not show significant differences in the concentrations of cotinine, cortisol, dehydroepiandrosterone, and testosterone. Moreover, significant positive correlations were noted between the concentrations in saliva samples collected with Salisoft® and those in saliva samples collected by passive drool.
Conclusion: This new device was shown to be suitable for saliva collection for the determination of the concentrations of cotinine and some steroids by enzyme immunoassay.

Assessment of Exposure to Polycyclic Aromatic Hydrocarbons in Japanese Children

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Objectives: To estimate the level of exposure to polycyclic aromatic hydrocarbons (PAHs) in Japanese children by urinary metabolite analysis and the possible contribution of soil ingestion and environmental tobacco smoke (ETS) to PAHs exposure.
Methods: Spot urine samples and questionnaire data were collected from 107 kindergarten children (3–6 years) and their mother. The urinary concentration of 1-hydroxypyrene (1-OHP), a biomarker of PAHs exposure, was measured using a high performance liquid chromatography-fluorescence detector.
Results: The geometric mean (GM) of urinary 1-OHP concentrations in children was 0.065 μmol/mol-cre (geometric standard deviation = 1.88). Parental smoking and time of playing outside (surrogate of soil exposure level) did not increase urinary 1-OHP level. Maternal urinary 1-OHP concentration correlated with, whereas GM (0.038 μmol/mol-cre) was significantly lower than, the urinary 1-OHP concentration in children. The latter might be attributable to greater amount of food intake per body weight for children than for adult.
Conclusions: The contribution of ETS and soil ingestion to PAHs exposure seemed to be small and thus they cannot be the major source of PAHs in Japanese children.