Reference C

Sample of Children's Cohort Studies

1. Japanese Studies

The Hokkaido Study of Environment and Children's Health (The Hokkaido Cohort Study)

Principal Investigator	Hokkaido University
Recruitment Period	2002–2005
Tracking Period	Age 5–6 years
Country	Japan
Sample Size	Approx. 20,000 (focus study: n=514)
Main Study Items−Exposures	Endocrine disruptors (maternal blood, umbilical cord blood, breast milk, hair)
Main Study Items−Outcomes	Congenital anomalies, birth weight, gestational age Allergies, neurodevelopmental and behavioral disorders
Purpose	Prospective cohort study for the purpose of monitoring congenital anomalies: particularly examination of risk factors for hypospadias and cryptorchidism and sensitivity to endocrine disruptors

The Tohoku Study of Child Development

Principal Investigator	Tohoku University
Recruitment Period	2001–2003
Tracking Period	Age 6–7 years
Country	Japan
Sample Size	Approx. 1,300
Main Study Items−Exposures	PCBs, methyl mercury, POPs, dioxins (mother's hair, maternal blood, umbilical cord blood, placenta, breast milk)
Main Study Items−Outcomes	Effect on development (NBAS, KSPD, BSID, FTII, K-ABC, other)
Purpose	Examine the effects of perinatal exposures of persistent organic pollutants (POPs) on the development of children

Japan Children's Study

Principal Investigator	Japan Science and Technology Agency
Recruitment Period	20052006 (started recruitment for longitudinal cohort study from 2007)
Tracking Period	―
Country	Japan
Sample Size	―
Main Study Items—Exposures	Growth environment study, behavioral observation, and brain image analysis
Main Study Items—Outcomes	Development
Purpose	To scientifically investigate methods and environments that better promote a balance of mental and physical development. The study is a central part of a research project by the Japan Science and Technology Agency (an independent administrative agency) that is focused on the growth of the brain and healthy development of mind, body, and language.

2. International Studies

The National Children's Study

Principal Investigator	U.S. Department of Health and Human Services (DHHS), National Institutes of Health (NIH), The Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD), The National Institute of Environmental Health Sciences (NIEHS), Centers for Disease Control and Prevention (CDC), and U.S. Environmental Protection Agency (EPA)
Recruitment Period	2008–2013
Tracking Period	Until age 21 years
Country	USA
Sample Size	100,000
Main Study Items−Exposures	• Physical environment (quality of home, community enviroment) • Chemical environment (insecticides, phthalates, heavy metals, air/water quality) • Biological environment (infection factors, endotoxins, diet) • Genetic influences (interaction of environmental factors and genetics) • Social factors (family, socioeconomic status, facilities, social network)
Main Study Items−Outcomes	• Outcome of pregnancy (premature delivery, congenital anomalies) • Neurodevelopment and behavior (autism, schizophrenia, learning disabilities) • Injuries (head injuries, hospitalization due to external injuries) • Asthma (development and worsening of asthma) • Obesity and physical development (obesity, diabetes, onset of puberty)
Purpose	To grasp the effects of environmental factors on the development of children and identify preventable factors. The study is implemented by seeking to verify preselected hypotheses, and examines the interactions of genetics and environmental factors including exposures in both pregnant women and mothers. The study will provide a solid foundation of data for diverse future studies and research, and will be an asset to the United States. The adoption of research that uses a cohort requires that the research be based on working hypotheses. For this purpose, the following 26 hypotheses (28 hypotheses at Nov. 2008) have been established for the study. ・ Congenital anomalies from impaired glucose metabolism of mothers ・ Increased risk of premature delivery from intrauterine exposure to mediators of inflammation ・ Increased risk of fetal growth restriction, premature delivery, congenital anomalies, and development disorders in children born through assisted reproductive technologies ・ Maternal subclinical hypothyroidism and neurodevelopmental disorders/adverse pregnancy outcomes ・ Non-persistent pesticides and poor neurobehavioral and cognitive skills ・ Prenatal infection and neurodevelopmental disorders

	• Genetic–environmental interactions and behavior • Prenatal and perinatal infection and schizophrenia • Family influences on child health and development • Impact of neighborhoods and communities on child health • Impact of media (television, Internet, games, etc.) exposure on child health and development • Social institutions (school and religious institutions) and child health and development • The role of prenatal maternal stress and genetics in childhood asthma • Exposure to indoor and outdoor air pollution, aeroallergens, and asthma risk • Dietary antioxidants and asthma risk • Social environmental influences on asthma disparities • Decrease in the risk of asthma due to early exposure to structural components and products of microorganisms • Obesity and insulin resistance from impaired maternal glucose metabolism • Obesity and insulin resistance from intrauterine growth restriction • Breastfeeding associated with lower rates of obesity and lower risk of insulin resistance • Fiber, whole grains, high glycemic index foods, and obesity and insulin resistance • Genetics, environmental exposures, and Type I diabetes • Repeated mild traumatic brain injury and neurocognitive development • Behavioral exposures, genetics, and childhood- or adolescent-onset aggression • Antecedents and resiliency to traumatic life events in childhood • Hormonally active environmental agents and reproductive development

Mothers and Children's Health and Environment (MOCHE) Study

Principal Investigator	MOCHE Coordinating Center, Ministry of Environment
Recruitment Period	2006–2010
Tracking Period	Until age 5 years (scheduled)
Country	South Korea
Sample Size	Recruitment of 500 mothers in first year only
Main Study Items—Exposures	Blood, biomarkers in urine (including lead, mercury, and cadmium) Environmental factors
Main Study Items—Outcomes	Effect on development, allergies, eczema, asthma, etc.
Purpose	To study the impact of environmental exposures on the health of mothers and children, and use the results to propose policies for environmental health.

The Norwegian Mother and Child Cohort Study (MoBa)

Principal Investigator	Norwegian Institution of Public Health
Recruitment Period	1999–2007
Tracking Period	Until age 6 years
Country	Norway
Sample Size	90,000 (from 1999 to September 2007)
Main Study Items—Exposures	Health, infection, nutrition, medication, occupation, lifestyle (alcohol, drugs, smoking, social status) • Banking of maternal blood and umbilical cord blood • Questionnaire-based study including dietary survey
Main Study Items—Outcomes	Pregnancy (childbirth, eclampsia, premature birth, low birth weight, congenital anomalies) Children (asthma, allergies, diabetes, cancer, polyarthritis, autism, ADHD)
Purpose	To collect as much data as possible concerning exposures and health outcomes, in order to respond to hypotheses that may arise in the future. The study is not aimed at proving specific etiological hypotheses.

Danish National Birth Cohort: Better Health for Mother and Child (BSMB)

Principal Investigator	Denmark Statens Serum Institut (Danish State Serum Institute)
Recruitment Period	1997–2002
Tracking Period	Tracking past adulthood (through use of registry systems)
Country	Denmark
Sample Size	101,042
Main Study Items—Exposures	No specific exposures set in advance Banking of maternal blood and umbilical cord blood Dietary survey, phone interviews with mothers
Main Study Items—Outcomes	Complications from pregnancy Childhood disease from early exposure Fetal development and determinants Effect of medication and infectious disease, etc.
Purpose	To learn about childhood disease and fetal development and their determinants from the perspective of complications at pregnancy and early exposures. The study places a particular emphasis on learning about the impacts of medication and infectious disease. The scope of the study covers all diseases that could be due to fetal exposures affecting childhood and beyond. The study establishes both a medication database and a biobank.

Generation R Study

Principal Investigator	Erasmus University Medical Center
Recruitment Period	2002–2006
Tracking Period	Until adulthood
Country	Netherlands
Sample Size	9,778 (n=1,232 for focus cohort study)
Main Study Items—Exposures	Biological factors (parents' traits, early growth, endocrine and immunocharacteristics, genetic background) Environmental factors (diet, parents' smoking, home) Social factors (parents' education, occupation, income, and marital status)
Main Study Items—Outcomes	Growth Behavior and development of cognitive skills Childhood disease Health care
Purpose	To identify environmental and genetic factors that impact development and health from the fetal period through adolescence. The study has four main areas of focus: (1) Growth and physical development, (2) behavior and development of cognitive skills, (3) childhood illness, and (4) health status and health management of pregnant women and children. The major purposes of the study are as follows: • Record growth from fetal period through adolescence • Identify biological, environmental and social factors that have an impact on growth from the fetal period through adolescence • Verify the effectiveness of current methodologies for early identification and prevention of high-risk groups

Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study

Principal Investigator	Utrecht University
Recruitment Period	1996–1997
Tracking Period	More than 8 years
Country	Netherlands
Sample Size	4,146 (n=855 for intervention study)
Main Study Items—Exposures	Indoor dust, distance from nearby roads, medication Diet
Main Study Items—Outcomes	Asthma, allergies
Purpose	To study the effect of reductions in allergens on childhood development of asthma, by recruiting mothers with allergic anamnesis and conducting a double-blind test of their children involving the use of mite-impermeable bedding. Also, to evaluate the role of environmental and dietary risk factors in relation to childhood development of allergic diseases, by recruiting mothers with and without allergic anamnesis and observing the development of asthma in their children.

3. Studies by International Organizations

Initiatives by the World Health Organization

The World Health Organization (WHO) since 2003 has operated an advisory committee for longitudinal cohort studies with funding from the U.S. National Institutes of Health (NIH), the Environmental Protection Agency (EPA), and the Centers for Disease Control (CDC). The advisory committee promotes mutual exchanges between researchers who are involved in longitudinal cohort studies in various countries, with a particular emphasis on assisting longitudinal cohort studies in developing countries. The aims of the advisory committee are to develop core protocols that can be commonly applied for longitudinal cohort studies to study the effects of the environment on the health and development of children, and to collect data in order to increase the value of information assets in each country.

Following are examples of hypotheses from current longitudinal cohort studies:

- There is a link between environmental exposures during early pregnancy and undesirable pregnancy outcomes such as congenital anomalies.
- Physicochemical and environmental causes have an impact on the sexual maturation of children.
- There is a link between childhood exposures to polluted air and increases in the risk of acute lower respiratory tract infection.
- There is a link between exposures to indoor air pollution and middle ear infections.
- There is a link between fetal exposures and increases in the risk of childhood cancer.
- Fetal and childhood exposures to heavy metals and other environmental pollutants with neurotoxic effects have a negative impact on neurodevelopment.

Following are examples of schemes from current longitudinal cohort studies:

- Sample-taking: Blood (maternal blood, paternal blood, children's blood, umbilical cord blood), amniotic fluid, placenta, meconium, urine (maternal urine, children's urine), sperm, hair, nail, mucous swab samples (oral, vaginal, and cervical), saliva, teeth, feces, and other environmental mediums
- Timing of sample-taking: At the time of enrollment, at second and third trimester, at birth, at 3/6/12 months, at each year of age, and other