Chapter 12
Birth Cohort Consortium of Asia (BiCCA): Current Children's Environmental Health Issues in Asia and Future Perspectives

Mei-Huei Chen, Sharon Ng, Meng-Shan Tsai, Ching-Chun Lin, and Pau-Chung Chen

Abstract Background: The environment is an important factor which not only may influence children's health at early life but also may lead to adverse consequences on later health. However, children in Asia are facing both traditional environmental hazards and new pediatric morbidities. A collaboration platform of Asian birth cohort studies to promote children's environmental health is warranted.

Methods: The Birth Cohort Consortium of Asia (BiCCA) was co-established in 2011 by the principal investigators of three birth cohorts in Asia including the Taiwan Birth Panel Study (TBPS), the Mothers and Children's Environmental

M.-H. Chen
Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan

Department of Pediatrics, National Taiwan University Hospital Yun-Lin Branch, Yunlin, Taiwan

Department of Pediatrics, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan

S. Ng
Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore, Singapore

M.-S. Tsai · C.-C. Lin
Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan

P.-C. Chen (✉)
Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan

Department of Environmental and Occupational Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

Department of Public Health, National Taiwan University College of Public Health, Taipei, Taiwan
e-mail: pchen@ntu.edu.tw

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Health Study (MOCEH), and the Hokkaido Study on Environment and Children's Health (Hokkaido Study). The related informations of environmental exposure and health outcome from participating cohorts have been published.

Results: Up to date (October, 2017), BiCCA includes 27 birth cohorts with approximately 80,000 study subjects that were conducted in 13 Asian countries. The geographical distribution of the cohort studies is uneven and assessment tools are diverse. Certain environmental neurotoxins have been identified; however, the exploration to critical environmental issues is not comprehensive. Targeted research collaboration is warranted and still ongoing.

Conclusions: The BiCCA provides an information exchange platform for birth cohort in Asian countries. Multidisciplinary collaboration and state-of-the-art technology application should initiate to identify specific regional environmental threats and improve the health of children in Asia.

Keywords Birth cohorts · Asia · Child environmental health

Abbreviations

BCSM	Birth Cohort Study in Mongolia—Towards Solving Global Problems in the Maternal and Child Health
BiCCA	Birth Cohort Consortium of Asia
BienHoa study	BienHoa Dioxin Cohort study
CHECK	Children's Health and Environmental Chemicals in Korea
CLHNS	Cebu Longitudinal Health and Nutritional Survey
COCOA	Cohort for Childhood Origin of Asthma and Allergic Diseases
DaDoCiV	Dioxin and Development of Children in Vietnam
DaNang study	DaNang Dioxin Cohort study
DOHaD	Developmental Origins of Health and Disease
EDC study	Environment and Development of Children Study
GUSTO	Growing up in Singapore Towards Healthy Outcomes
HBC study	Hamamatsu Birth Cohort for Mothers and Children
Hokkaido study	Hokkaido cohort: Hokkaido Study on Environment and Children's Health
HRBC	Harvard Reproductive and Birth Cohort
KCHS	Kalutara Children's Health Study
LWBC	Laizhou Wan Birth Cohort
MISC	Mother-Infant Study Cohort
MOCEH	Mothers and Children's Environmental Health Study
Nepali	Nepali Birth Cohort Study in Chitwan Valley
NJMUBC	Nanjing Medical University Birth Cohort
PCBs	Polychlorinated biphenyls
PFASs	Perfluoroalkyl substances
PSKC	Panel Study on Korean Children

Sapporo study	Sapporo cohort: Hokkaido Study on Environment and Children's Health
SBC	Shanghai Birth Cohort
TBPS	Taiwan Birth Panel Study
TEC	Taiwan Early-Life Cohort
TMICS	Taiwan Maternal and Infant Cohort Study
TSCD	The Tohoku Study of Child Development
UGAAR	Ulaanbaatar Gestation and Air Pollution Research
USM Pregnancy Cohort Study	Universiti Sains Malaysia Pregnancy Cohort Study

12.1 Introduction

The World Health Organization (WHO) had reported that 23% of global deaths and 26% of deaths among children under 5 are due to modifiable environmental factors [1]. Children's environmental health issues may vary widely with regional development but may also be affected by globalization simultaneously. Asia contains more than half of children population in the world. The general environmental factors such as climate, geography, ethnic, and cultures diverse greatly. Moreover, poor, wealthy, underdeveloped, or rapid industrialization countries are all included in this area. Coexistence of traditional environment hazards and new emerging threats is a complex challenge. These phenomena highlight the uniqueness and importance of children's environmental health in Asia [2, 3].

12.2 Child's Environmental Health Burden

The burden of environmental-related disease is unevenly distributed, with greatest exposure to children in developing or low-income countries. Although the primary health issues of children in developing countries are low birth weight, malnutrition, and infectious diseases, they are also facing new pediatric morbidity including allergic diseases, neurobehavioral problems, and overweight and obesity same as children in developed countries [4, 5]. On the other aspect, traditional environmental hazards such as unsafe water, contaminated food, and myriad of toxic chemicals are major threats to children in developing countries, while environmental tobacco smoke, air pollution, and food-related persistent and nonpersistent endocrine-disruptive chemical exposure attract more attention in developed countries. Nevertheless, the aforementioned boundaries (or classifications) have been broken due to the relocation of heavy and traditional industries into developing countries and frequent international exchanges. The circulation of dust, air, water, and food chain all facilitate the ubiquitous distribution of air pollutants, persistent organic pollutants, or contaminants of emerging concern that originate from industrialization. Therefore, children's environmental health is both of regional and global importance.

12.3 Role of Birth Cohort Studies

The foundation to promote environmental child health in Asia is to recognize the major environmental threats in each specific region or country, figure out their temporal trends, and establish the scientific evidences for their health hazards. Birth cohort is an ideal design to investigate health outcomes following environmental exposure during critical developmental period. In Asia, some birth cohort studies have lasted for years and contributed to important scientific issues such as environmental tobacco smoke. Until recently, the necessity of nationwide or large-scale birth cohorts has been emphasized as well. It's the optimal timing to establish a collaboration platform for Asian birth cohorts. Information derived from preexisting studies may be harmonized by redefined standardized exposure and outcome variables. Integration should increase statistical power through an enlarged set of data, allowing the researcher to examine rare events or strengthen the scientific evidence of causality. The pathogenesis of environmental toxicants could be further explored via comparisons between diverse exposure levels and genetic variation derived from different studies. The unsolved issues and priority could be identified. The updated or consensus of methodology for exposure and outcome assessments may further provide foundation for next-generation or nationwide birth cohorts. The ultimate goal is to translate scientific knowledge derived from multiple studies or countries to policy-making or strategy implementation to promote environmental health of children in Asia and beyond.

12.4 Birth Cohort Consortium of Asia (BiCCA)

The Birth Cohort Consortium of Asia (BiCCA) was co-established in 2011 by the principal investigators (PIs) of the following three birth cohorts in Asia: the Taiwan Birth Panel Study (TBPS) from Taiwan (PI: Chen), the Mothers and Children's Environmental Health Study (MOCEH) from Korea (PI: Ha), and the Hokkaido Study on Environment and Children's Health (Hokkaido Study) from Japan (PI: Kishi). The aims are to facilitate the exchange of knowledge and collaboration between cohorts and researchers and to explore the future needs of children in Asia. Several symposia/seminar, workshop, and PI meetings were held to build capacity related to inclusion criteria, inventory, profile paper, and organization bylaws.

Up to date (October, 2017), BiCCA includes 27 birth cohorts with approximately 80,000 study subjects that were conducted in 13 Asian countries (Fig. 12.1), including China (3 cohorts), Japan (4), Malaysia (1), Mongolia (2), the Philippines (1), the Republic of Korea (5), Singapore (1), Taiwan (3), and Vietnam (3) in

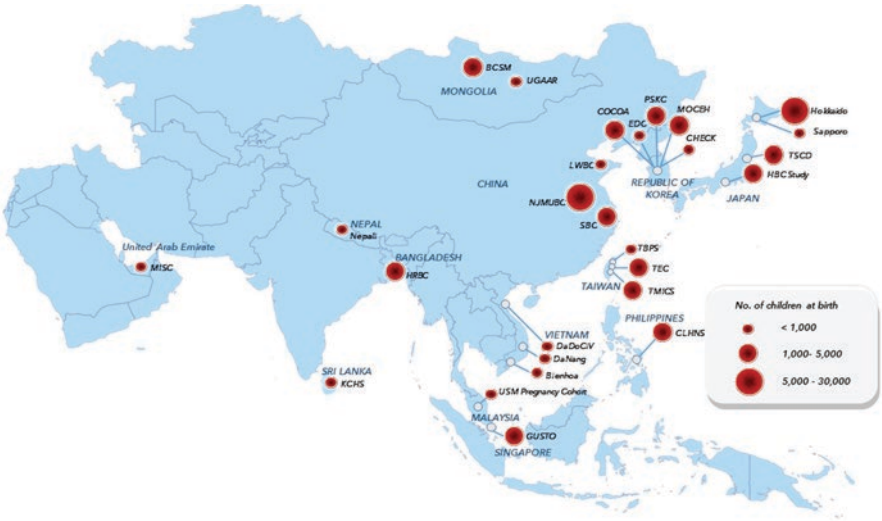

Fig. 12.1 Asian birth cohort studies collaborating in BiCCA. Adapted from Kishi R. et al. Birth cohort consortium of Asia: current and future perspectives. Epidemiology 2017

Western Pacific Region; Bangladesh (1), Nepal (1), and Sri Lanka (1) in the Southeast Asia Region; and the United Arab Emirates (1) in the Eastern Mediterranean Region. The enrolment period and numbers of participants of each cohort varied widely. The oldest cohort, CLHNS (Cebu Longitudinal Health and Nutritional Survey), was established in 1983, while the newest one, MISC (Mother-Infant Study Cohort), was started since 2015. Most of the cohorts recruited mothers during pregnancy or at birth. The only two preconception cohorts were NJMUBC (Nanjing Medical University Birth Cohort) and SBC (Shanghai Birth Cohort) from China, and biosamples from biological father were collected. COCOA (Cohort for Childhood Origin of Asthma and Allergic Diseases) also collected blood and DNA of the biological father. Cohorts in Malaysia, Nepal, and Vietnam recruited only 100–200 participants; NJMUBC established since 2014 planned to enroll 30,000 mother-infant pairs [6]. While most of the cohort studies in BiCCA focused on environmental pollutants, BCSM (Birth Cohort Study in Mongolia—Towards Solving Global Problems in the Maternal and Child Health), CLHNS, GUSTO (Growing up in Singapore Towards Health Outcomes), MISC, Nepali (Nepali Birth Cohort Study in Chitwan Valley), and USM Pregnancy Cohort Study (Universiti Sains Malaysia Pregnancy Cohort Study) were designed to investigate the role of nutrients. Those cohorts were marked as gray column in Table 12.1. GUSTO even performed comprehensive measurements of body composition of children including skinfolds and magnetic resonance imaging.

Table 2.1 Measurements of selected environmental exposure and nutrients intake of participating studies in Birth Cohort Consortium of Aisa

Nation	Cohort Name	Outdoor air pollutions	Tobacco smoke[a]	Heavy metals[b]	Diet and nutrition[c]	Pesticides	POPs	non-POPs EDC
BANGLADESH	HRBC			Arsenic				
CHINA	LWBC			v	v	v	v	v
	NJMUBC	v	v	v	v	v	v	v
	SBC			v	v	v	v	v
JAPAN	HBC Study				v			
	Hokkaido		v		Folate only		v	v
	Sapporo		v	Mercury	v	v	v	v
	TSCD			v	v	v	v	
KOREA	CHECK			v	v	v	v	v
	COCOA	v	v		v			v
	EDC study	v	v	v	v		v	v
	MOCEH	v	v	v	v			v
	PSKC		v					
MALAYSIA	USM Pregnancy Cohort		v		v			
MONGOLIA	BCSM				Fish intake only			
	UGAAR	v						
NEPAL	Nepali			v	v			
PHILIPPINES	CLHNS				v			
SINGAPORE	GUSTO	v	v		v			
SRI LANKA	KCHS	v						
TAIWAN	TBPS		v	v	v	v	v	v
	TEC	v		v	v		v	
	TMICS		v	v	v	v	v	v
VIETNAM	BienHoa study						dioxin	
	DaDoCiV						dioxin	
	DaNang study						dioxin	
UNITED ARAB EMIRATE	MISC				Infant feeding practices			

Those cohorts designed to investigate the role of nutrients were marked with a gray column

[a]Biomarker measurement available

[b]Metals such as aluminum, antimony, arsenic, barium, beryllium, cadmium, cesium, chromium, cobalt, gallium, lead, mercury, molybdenum, nickel, platinum, thallium, thorium, tungsten, and uranium are included

[c]Essential elements such as manganese, zinc, copper, selenium, and iron

12.5 Brief Summary of Cohort Characteristics

Table 12.1 shows the selected environmental exposure of participating studies in BiCCA. Certain cohorts target their studies on specific environment pollutants, for example, Harvard Reproductive and Birth Cohort (HRBC) in Bangladesh investigated the impact of arsenic exposure, Ulaanbaatar Gestation and Air Pollution Research (UGAAR) Study in Mongolia explored the health effects of air pollution, the Kalutara Children's Health Study (KCHS) in Sri Lanka focused mainly on exposure to PM2.5 and black carbon, and three small cohorts in Vietnam focused on toxicity of dioxin. Cohorts in Japan, Korea, and Taiwan concern not only on traditional environmental hazards such as heavy metals and/or pesticides but also on persistent organic pollutants or other endocrine disrupters. Exceptions are Hamamatsu Birth Cohort for Mothers and Children (HBC) study in Japan which investigated the trajectories of children neurodevelopment and the Panel Study on Korean Children (PSKC) which aims to collect data on the characteristics of children's growth and development. Cohorts in China, one of the fastest growing economies, were established within the recent 5 years and do consider a variety of environmental pollutants. As expected, tobacco smoke is a universal concern regardless of status of industrialization or urbanization. Although only one third of cohorts record outdoor air pollution, the health hazards of these transboundary pollutants need special attention.

12.6 Knowledge Derived from BiCCA

Bicca provide the very first step to integrate the public information related to birth cohorts in Aisa on public. With this platform, we found that the geographical distribution of the cohort studies is uneven and exploration to critical environmental issues is not comprehensive. The experiences of developed countries to deal with traditional pollutants are worth sharing such as removal of lead from gasoline, the mercury pollution reduction project, and antismoking campaigns [2]. Meanwhile, contaminants of emerging concern, outdoor air pollution, or climate change could be the future common enemy for children in Asia. Despite the main health issues focusing on fetal growth, pregnancy outcome, growth and obesity, allergic disease and immune function, neurodevelopmental and behavioral problems, and endocrine function, the diverse assessment tools for neurobehavioral status could be the largest challenge. A recent review summarized relevant epidemiologic evidence for cohorts in Asia and points out the potential neurotoxicity of mercury, environmental tobacco smoke, polychlorinated biphenyls (PCBs), and perfluoroalkyl substances (PFASs) on children [7]. The initiation of targeted research collaboration within BiCCA and data harmonization has started. The BiCCA still welcomes birth cohorts in Asia to join us. Enquiries and initial approaches regarding membership or detailed information are welcome (http://www.bicca.org/).

12.7 Future Perspective Through Collaboration

Traditionally, the paradigm of Developmental Origins of Health and Disease (DOHaD) has focused on influences of nutrition status during early life on health across the lifespan. Environmental child health research have specifically investigated exposure to unfavorable chemicals from environmental or occupational setting during prenatal and/or early postnatal period and its impact on the occurrence of diseases later. Nevertheless, co-exposure and interactions between nutrient elements, environmental toxicants, and genetic variation are a reality in the living environment. For instance, predator fish consumption provides a variety of essential nutrients such as polyunsaturated fatty acid and selenium but also has been recognized as one of the major sources of persistent organic pollutants including methylmercury, PFASs, dioxin, and dioxin-like compounds in the general population [8]. Combined data from Taiwanese and Korean birth cohorts showed that fish consumption and cord blood mercury level influenced birth weight at opposite direction by path analysis [9]. In addition, early life events especially during the critical fetal development period predispose not only to childhood illness but also to increased risk of adulthood morbidity and mortality. Accumulating evidences have supported that maternal medical conditions (e.g., preeclampsia, gestation diabetes mellitus, anemia, etc.), malnutrition, in utero exposure to environmental tobacco smoke, heavy metals, and endocrine-disruptive chemicals may affect fetal growth [10, 11] and may be associated with increased risk of low birth weight [12] and

non-communicable diseases in adulthood. The concept of exposome, which refers to measures that reflect all exposure events of an individual during a lifetime and how those exposures relate to disease, provides new insight to cope with the health research related to the beneficial effect of nutrients and toxic effect of environmental pollutants [13]. Along with the advancement of "omic" technologies, the exploration of biological functions such as DNA methylation or microbiome pattern that are influenced by maternal or fetal exposome becomes feasible and should contribute to the understanding of causal relationship between exposure and health.

12.8 Challenge of Child's Environmental Health Research

Prevention is the core concept of children's environmental health. However, low-dose multipollutant exposure in human daily life is unavoidable; even the regulation of toxic chemicals or workplace safety control decreases the incidence of severe intoxication or high-dose environmental contamination. In regard to health hazard, the effect for single pollutant exposure may be small, but the impact of mixture exposure is usually unknown and lacks scientific evidence. Furthermore, the differences of individual susceptibility and gene-environment interaction are challenges for clinical assessment of environmental threats. Unlike a specific causal-relationship as infectious pathogen and disease, the role of environmental pollutans on the occurence of disease could be only one of the causative or trigger factors. Co-existance with other adverse factors such as life style are needed to affect health. The exposure factor for risk assessment varies by physiological and behavioral differences among different age groups [14]. These uncertainties may underestimate the health effects of environmental pollutants, especially for vulnerable pregnant women and children. Ultimately, how to apply the state-of-the-art technique in analysis and risk assessment in preventing children's environmental threats is the key of knowledge translation to implementation.

12.9 Conclusions

The establishment of BiCCA provides a platform for information exchange related to basic characteristics, environmental exposure measurements, and outcome assessment of birth cohorts in Asia. Therefore, a multidisciplinary collaboration with different professionals has to be initiated, not only the integration of preexisting knowledge but also the application of state-of-art technologies to maximize the advantage of the birth cohort research design. Ultimately, these efforts should contribute to improving children's environmental health.

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