Chapter 2
DOHaD Cohort Studies and Public Health Implications in Japan

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Abstract Because the "Developmental Origins of Health and Disease (DOHaD)" hypothesis recently became widely known in a medical research area, fetal and childhood environment has been drawing more attention. In addition, based on the DOHaD, childhood growth trajectories, which are described by multilevel analysis, might be important in examining the effects of early-life environment. Therefore, it becomes more important to establish epidemiological evidence related to DOHaD from population-based birth cohort studies which include the study that uses the dataset from some public health activities. Moreover, it is also important to apply the findings from these studies to public health. In this chapter, some nationwide and local birth cohort studies and the results related to DOHaD from these studies are introduced. For instance, the association between maternal smoking status during pregnancy and birthweight from "Japanese Environment and Children's Study" which is conducted by the Ministry of Environment, and childhood growth trajectories according to maternal smoking status during pregnancy from Project Koshu, are described.

Keywords Birth cohort study · Public health · Japan

Abbreviations

BMI	Body mass index
CI	Confidence interval
DM	Diabetes mellitus
DOHaD	Developmental Origins of Health and Disease

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GDM	Gestational diabetes mellitus
HG	Hyperemesis gravidarum
JECS	Japan Environment and Children's Study
LBW	Low birth weight
NS	Never-smokers
NVP	Nausea and vomiting in early pregnancy
OR	Odds ratio
PIH	Pregnancy-induced hypertension
SD	Standard deviation
SGA	Small-for-gestational-age
SM	Current smokers

2.1 Introduction

In recent years, the "Developmental Origins of Health and Diseases" hypothesis, in addition to the established "fetal programming" and "Barker's hypothesis," has been suggested to clarify the mechanisms of childhood growth and development [1]. These were described as an example of the association between a specific path of growth—consisting of slow growth in fetal life and rapidly increasing body mass index (BMI) as an infant—and the development of adulthood chronic diseases [1–5]. Thus, appropriate fetal growth, a crucial element of these hypotheses, is considered an important factor for the future health of an individual. Some perinatal outcomes, such as low birth weight (LBW) and intrauterine growth restriction, are considered indicators of inappropriate fetal growth. However, descriptions of the study participants from the fetal period are necessary to examine these hypotheses or concepts, and it is difficult to collect information on the fetal period in a timely matter in most birth cohort studies, as participants of these studies are usually recruited after birth, and information on the prenatal period (e.g., maternal lifestyle habits during pregnancy) is collected retrospectively. For instance, in Japan, Ministry of Health, Labour and Welfare is carrying out a nationwide birth cohort study called as "Longitudinal Surveys of Newborns in the twenty-first Century (born in 2001 (the 2001 survey) and 2010 (the 2010 survey))" which are based on birth registration data of vital statistics [6]. These surveys were commenced at birth of participants. Thus, it was impossible to timely obtain the information before birth although the data might be highly representative Japanese population. Therefore, it is necessary to consider some information biases and measurement errors in these studies.

Because it is important to obtain accurate descriptions of maternal and child health status to minimize these biases and errors, recent studies like "Japan Environment and Children's Study (JECS)" have begun during the early pregnancy period [7]. Prior to these recent studies, an ongoing prospective cohort study of pregnant women and their children was initiated in a Japanese rural area called "Project Koshu." Previously, I reported the overview of this study [8]. Although this study has several limitations (e.g., relatively small sample size), some articles have examined the association between fetal environment and childhood growth using the dataset of this study [9–18]. For instance, the relationship between maternal smoking during pregnancy and childhood growth, especially as it pertains to childhood obesity, was examined [9, 11–13].

Because these studies are basically carried out in community settings, it might be relatively easy to apply the results from these studies to public health activities not only in a local area but also a country level. In this chapter, some population-based cohort studies and some findings from these studies which could feedback to the communities are introduced.

2.2 Project Koshu

2.2.1 The Overview of Project Koshu

The Koshu city (formerly Enzan city) administration office and Department of Health Sciences, Interdisciplinary Graduate School, University of Yamanashi cooperatively conduct an ongoing prospective cohort study of pregnant women and their children called Project Koshu, which commenced in 1988. Koshu city is located in the center of Japan. The population of Koshu city is 33,000, with approximately 200 births each year. We expected a high follow-up rate in this project because most of the children do not migrate elsewhere until graduation from junior high schools.

In Japan, pregnant women are encouraged to register their pregnancy at the city office, and their children must be registered. In addition, after birth, children are invited to undergo a medical checkup at ages 1.5, 3, and 5 years. First, to ascertain the lifestyle habits of expectant mothers, we conducted a questionnaire-based survey with expectant mothers who visited the city office to register their pregnancies. Informed consent was obtained prior to the survey. In the study area, over 80% of expectant mothers registered their pregnancy in the first trimester, and almost all registered by 18 gestational weeks. Next, at each medical checkup of the children born to these mothers, we surveyed the lifestyle habits of the children and their mothers by using a questionnaire. Subsequently, at each medical checkup for the children, data on children's growth and physical characteristics were collected, in addition to anthropometric data from elementary and junior high school children, which are measured annually in April, for each grade, according to the Japanese School Health and Safety Law. Therefore, childhood anthropometric data were repeatedly obtained.

Originally, the purpose of this cohort study was to describe current status of maternal and child health in the area. For example, a trend of maternal smoking during pregnancy was previously reported [16]. Then, after accumulating the data from each year, longitudinal datasets were created to examine the association between exposures in fetal and infant periods, such as maternal smoking during pregnancy or childhood sleep duration and childhood growth and development. Thus, depending on the research question, various cohorts could be established. The scheme of Project Koshu is presented in Fig. 2.1.

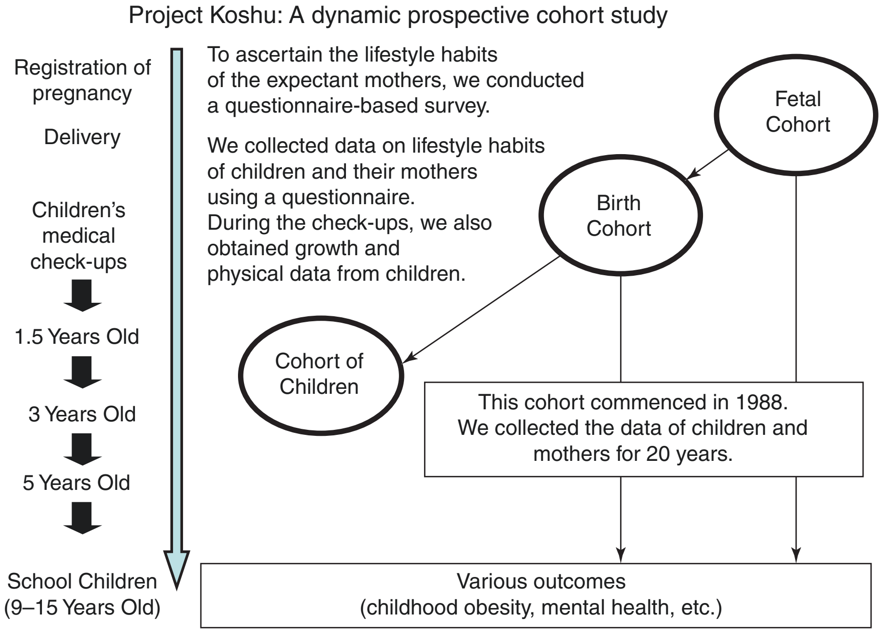

Fig. 2.1 Brief study design of Project Koshu (original data: Suzuki, 2015 [8])

In order to ensure confidentiality, the mothers and children were identified by unique numbers to match the data obtained from the early pregnancy survey and the later medical checkups. This cohort study was approved by the Ethical Review Board of the University of Yamanashi, School of Medicine, and was conducted in accordance with the Guidelines Concerning Epidemiological Research (the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour and Welfare, Japan). Written informed consent from the participants was obtained.

2.2.2 Some Findings Related to DOHaD from Project Koshu

Maternal smoking during pregnancy is a major cause of low birth weight and intrauterine growth restriction [19–22]. This association has been confirmed in this area [9]. In addition, it has been suggested that maternal smoking cessation before or during early pregnancy may still allow for appropriate fetal and childhood growth [15]. In addition, Mizutani et al. examined the association between maternal lifestyle factors, including smoking during pregnancy, skipping breakfast and short sleep duration, and childhood obesity [9]. This may have been the first article to examine the effect of maternal smoking on childhood obesity in Japan. Maternal smoking habits were significantly associated with overweight (adjusted odds ratio

(OR), 2.2; 95% confidence interval (CI), 1.1–4.1) and obesity (adjusted OR, 3.9; 95% CI, 1.5–10.6) among 5-year-old children [9]. Then, my colleagues and I examined whether the association persists up to 9–10 years of age [11]. However, these point estimates at the age of 9–10 years were considerably lower than those observed at 5 years [11].

Next, we examined the association between maternal smoking during pregnancy and overweight in childhood during different periods using two cohorts from the same population: birth cohort (the first cohort) and non-overweight children at 5 years of age (the second cohort) because there were some differences in adjusted ORs for maternal smoking during pregnancy, which affected the differences observed in childhood obesity/overweight between 5-year-old and 9–10-year-old children [14]. An association between maternal smoking during pregnancy and overweight only in male children in the first cohort analysis (adjusted OR, 4.5; 95% CI, 2.0–10.2) was observed. It is suggested that the effects of maternal smoking during pregnancy on childhood overweight tend to appear before 5 years of age, especially in male children [14].

On the other hand, the term "life course epidemiology" has recently become popular. As previously described, Barker's hypothesis and the DOHaD hypothesis are probably the best-known examples of a life course association. Because these state that poor fetal nutrition, indicated by small birth size, leads to fetal adaptations that alter the propensity to adult diseases [23], it is necessary to describe the growth trajectories during childhood. However, there was no study to carry out such an analysis to clarify the association between maternal lifestyle during pregnancy, which is used as a proxy indicator of fetal environment, and childhood growth or development. Twisk stated that multilevel analysis is usually suitable for analyzing correlated data [24]. Then, my colleagues and I examined the gender differences in the association between maternal smoking during pregnancy and later growth in childhood by conducting a multilevel analysis (a fixed effects model) [12]. The mean birth weight of children whose mothers had smoked during pregnancy was significantly lower than the birth weights of children born to non-smoking mothers [12]. Subsequently, childhood BMI at each checkup age significantly increased but only among male children born to smoking mothers [12]. Furthermore, it was observed that this increase continued after 3 years of age (Fig. 2.2) [12].

Next, Zheng et al. described gender-based height growth patterns in Japanese school-aged children using a multilevel analysis, as determining standard pubertal growth patterns using longitudinal anthropometric measures is important in growth assessment [17]. Height was similar between genders at 6.5–9.5 years of age [17]. Then, girls grew faster and were taller than boys at 10.5–11.5 years of age [17]. Subsequently, boys caught up and exceeded girls' heights starting at age 12.5 [17]. Height gain trajectories showed that the girls' annual height gains increased slowly and peaked from 9.5 to 11.5 years of age, while boys' height gains declined slightly at first and peaked at 11.5–12.5 years of age [17]. The gender-based differences in height gains were significant from 7.5 to 14.5 years of age ($p < 0.0001$) [17]. Growth rate and height gain trajectories were similar between genders, although pubertal growth spurts were observed earlier in girls than in boys [17]. Moreover, Wei et al.

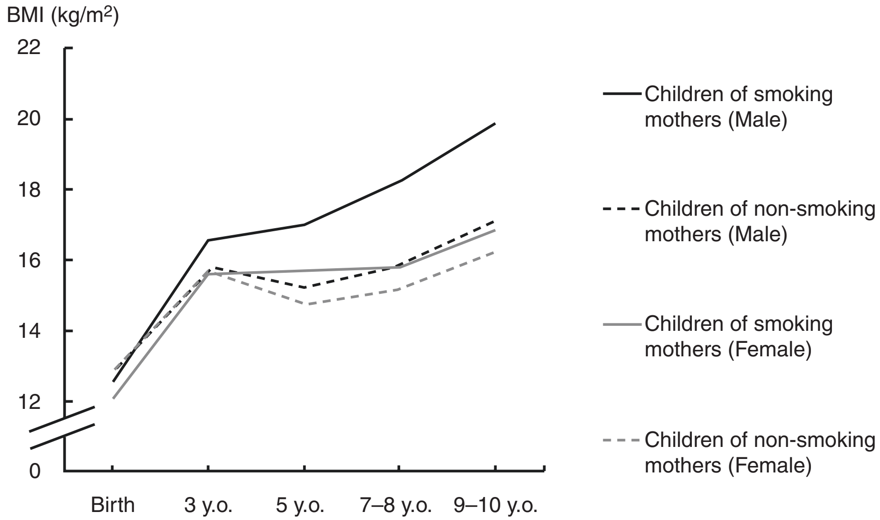

Fig. 2.2 Children's body mass index trajectories by maternal smoking status during pregnancy, calculated by individual growth analysis (original data: Suzuki, 2015 [8])

examined the differences in growth patterns during adolescence between overweight/obese and non-overweight children in Japan [18]. Overweight/obese girls grew taller in the first half period, reached their peak height gain about a year earlier than non-overweight girls did, and experienced an earlier decrease in height gain [18]. Similarly, it was initially observed that overweight/obese boys gained more height than non-overweight boys did [18]. Additionally, non-overweight boys maintained a higher rate of height gain from the age of peak height gain, although the age of peak height gain did not differ between the two groups [18].

Finally, we conducted a kind of pathway analysis between maternal smoking during pregnancy and infancy growth. As a result, maternal smoking during pregnancy contributed to lower birth weight as well as previous findings [25]. In addition, lower birth weight contributed significantly to rapid infancy growth. Maternal smoking during pregnancy was also related to infant growth through breastfeeding status during the first 3 months [25]. The indirect standardized effect of maternal smoking through the three pathways was 0.04 [25]. In addition, maternal smoking was also directly linked to rapid infancy growth. The standardized direct effect was 0.06 ($p = 0.002$) [25]. Taking all the pathways into account, the standardized total effect of maternal smoking on infancy growth was 0.11 [25]. It was suggested that maternal smoking during pregnancy may both indirectly, through birth weight, breastfeeding status, and directly influence rapid infant growth; further, other pathways have not yet been identified (Fig. 2.3).

Because this cohort study is conducted only in a rural area in Japan, there are some limitations. For example, it is necessary to consider statistical power because, as mentioned above, the number of annual births is relatively small. In addition, there are few clinical information because this study was community-based.

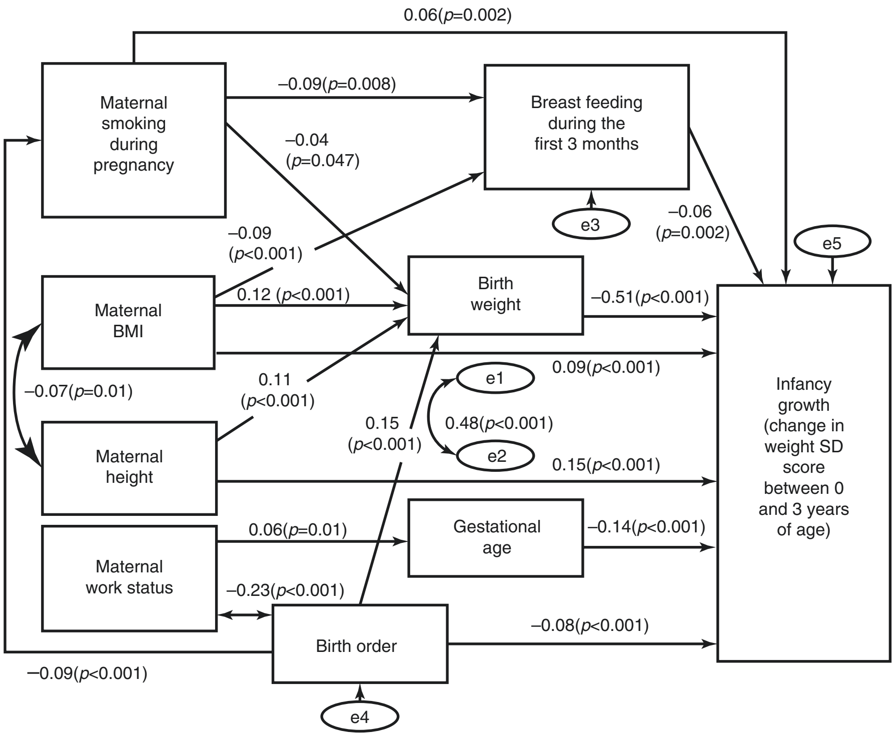

Fig. 2.3 Standardized pathways between maternal smoking during pregnancy and infancy growth determined using exploratory methods (original data: Zheng et al., 2015 [25])

However, the issue about selection bias might be small because the follow-up rate is approximately 80% at 10 years of age [12]. Thus, it might be important to establish some evidence about DOHaD from this kind of small community-based cohort study because the feasibility might be relatively higher than the large cohort study like JECS.

2.3 Longitudinal Surveys of Newborns in the Twenty-First Century (2001 Cohort and 2010 Cohort)

2.3.1 The Overview of Longitudinal Surveys of Babies Born in the Twenty-First Century

This national representative prospective cohort studies were conducted by the Ministry of Health, Labour and Welfare. The overview of the survey was described in some related articles [26–28]. First, children born between January 10 and 17, 2001, and between July 10 and 17, 2001, and their fathers and mothers were recruited for the 2001 survey based on the information of birth registration data in vital statistics (n = 53,575). On the other hand, children born between May 10 and 24, 2010 were recruited for the 2010 survey in the same method for the 2001 survey (n = 43,767). These data were linked with the birth registration record data of vital statistics. A total of 47,015 and 38,554 respondents participated in the first survey which was conducted in 2001 and 2010, respectively.

In the first survey, guardian, household, employment (including child care leave), working hours, sharing in household chores and child rearing by parents, housing conditions, efforts and attempts in child rearing, advantages of having the baby, disadvantages of having the baby, worries and anxieties about child rearing, breastfeeding, income, maternal smoking status after delivery (6 months later), and maternal and paternal educational backgrounds (the first follow-up survey) were collected by the questionnaire. At each annual survey, the contents of questionnaires were slightly changed based on childhood growth and development. On the other hand, sex of the children, birth weight, gestational weeks, birth order, nationality of mothers and fathers, and maternal age at their delivery were collected by birth registration data.

All respondents consented to the purpose of these surveys described by the Ministry of Health, Labour and Welfare. Moreover, the data of this survey was completely anonymized and de-identified by the government when the data was provided to the researchers who were permitted to use by the government.

Some of the results of each survey were described in the website of the Ministry of Health, Labour and Welfare [6].

2.3.2 Some Findings Related to DOHaD from Longitudinal Survey of Newborns in the Twenty-First Century

As mentioned above, because it is essential to be obtained permission to use the data of survey by the government, the number of articles by using the data of this survey was relatively limited. In addition, it is relatively difficult to examine the effect of factors during fetal period on childhood growth and development because these surveys were commenced at birth. However, there were some valuable findings from the surveys.

First, because it has been suggested that socioeconomic status was associated with healthy lifestyle, such as nutrition, physical activity, and smoking status [29–31], socioeconomic status might be an important factor which is associated with DOHaD. Fujiwara et al. examined the impact of income inequality and parental socioeconomic status on several birth outcomes [26]. It was observed that higher prefectural income inequality was associated with z-score of birth weight for gestational age, but not with only gestational age in multilevel analysis [26]. In addition, there was significant association between parental educational level and the z-score of birth weight for gestational age and small-for-gestational-age status [26].

Next, regarding childhood physical growth, Franchetti and Ide described the trajectories of childhood BMI, especially focused on adiposity rebound, and examined the association between sociodemographic and lifestyle factors and childhood growth [27]. As a result, after controlling for sex, obese children had a 48.5% higher hazard to experience AR than nonobese children by Cox's proportional hazards model [27]. In addition, the difference in BMI transition between obese and nonobese children was also captured by description of trajectories [27]. Regarding the sociodemographic and lifestyle factors, children who had a longer gestational period were likely to be lower BMI [27]. On the other hand, children who received parental care from nonfamily members were likely to be higher BMI [27].

Finally, Higa Diez et al. described the association between preterm birth and childhood behavioral outcomes (three attention problems and four delinquent/aggressive behaviors) at 8 years of age [28]. In logistic regression model, positive associations were observed between preterm birth (<37 weeks) and adverse behavioral outcomes compared with full-term birth (39–41 weeks) [28]. For attention problems, it was suggested that preterm birth was significantly associated with "inability to wait for his/her turn" [28]. It was suggested that preterm birth is significantly associated with increasing risk of behavioral problems related to attention and delinquent/aggressive behavior at 8 years old [28].

Although these results were only based on the survey of 2001 cohort, it is possible to use the data of 2010 cohort which is almost similar items to the survey of 2001 cohort. Therefore, it might be possible to compare the childhood outcomes or the associations between sociodemographic and lifestyle factors and these outcomes between two surveys. In the future, some valuable findings related to DOHaD, especially the effect of childhood lifestyle and environment, during early infancy period might be produced.

2.4 Japan Environment and Children's Study (JECS)

2.4.1 The Overview of Japan Environment and Children's Study (JECS)

For JECS, pregnant women were recruited between January 31, 2011 and March 31, 2014. Eligibility criteria for participants (expectant mothers) were as follows: (1) residing in the study area at the time of recruitment, (2) expected delivery date after August 1, 2011, and (3) capable of comprehending the Japanese language and completing the self-administered questionnaire. Individuals residing outside the study area who attended cooperating healthcare providers within the study area were excluded from the study. Details of the JECS project have been described in a previous article [7]. The response rate of JECS was about 79% [32]. Because the recruitment period was relatively long, there were some datasets which included not only all participants but also a part of participants. For example, we used the first fixed dataset named as "jecs-ag-ai-20131008 dataset," which was released in October 2013. Detail of this dataset was published previously [33]. This dataset consisted of information on 9369 singleton infants born before December 31, 2011 [34]. The mean age and standard deviation (SD) of participants in this dataset was 31.0 ± 5.0 years [34]. The mean gestational duration and SD at their pregnancy registration was 108.6 ± 42.7 days [34]. Recently, the complete dataset at birth has been released and distributed to the JECS researchers.

The JECS protocol was approved by the Institutional Review Board on epidemiological studies of the Ministry of the Environment and the Ethics Committees of all participating institutions: the National Institute for Environmental Studies which leads the JECS, the National Center for Child Health and Development, Hokkaido University, Sapporo Medical University, Asahikawa Medical College, Japanese Red Cross Hokkaido College of Nursing, Tohoku University, Fukushima Medical University, Chiba University, Yokohama City University, University of Yamanashi, Shinshu University, University of Toyama, Nagoya City University, Kyoto University, Doshisha University, Osaka University, Osaka Medical Center and Research Institute for Maternal and Child Health, Hyogo College of Medicine, Tottori University, Kochi University, University of Occupational and Environmental Health, Kyushu University, Kumamoto University, University of Miyazaki, and University of the Ryukyus. The JECS was conducted in accordance with the Helsinki Declaration and other nationally valid regulations and guidelines.

Information of mothers and their partners during the mothers' pregnancy was collected by questionnaire during the first and second trimesters of pregnancy [7]. The questionnaire included questions about lifestyle factors (stress levels, diet, smoking habits, alcohol consumption, physical activity, sleeping patterns, infections, and medication), SES, and physical environment (heat, ionizing radiation, housing conditions, and neighborhood) [7]. Maternal anthropometric data before pregnancy and data on maternal weight gain during pregnancy and complications before and during pregnancy including pregnancy-induced hypertension (PIH), diabetes mellitus (DM) and gestational diabetes mellitus (GDM), history of previous pregnancy, sex of infants, birth order, and perinatal outcomes such as birth weight and gestational duration were also collected from medical records, which were provided by their obstetricians [7].

2.4.2 Some Findings Related to DOHaD from JECS

Because JECS is relatively new birth cohort study, only few articles which used the fixed data were published. Moreover, it is difficult to confirm childhood outcomes after birth because it took only approximately 1 year after the final birth of participants. In this section, I introduce two articles which used the fixed dataset of JECS.

First, although there were a lot of articles to describe the association between maternal smoking during pregnancy and birthweight, to the best of our knowledge, there have been no large nationwide population-based epidemiological studies examining the association that simultaneously controlled for clinical information, SES, pregestational BMI, and maternal weight gain during pregnancy. Thus, we described the association between maternal smoking status during pregnancy and birth weight while taking these confounding factors into consideration [34]. Our analysis utilized the first fixed dataset from JECS. After controlling for potential confounding factors, maternal smoking status during pregnancy was significantly associated with birth weight [34]. There was a significant difference in birth weight between NS and SM for both male and female infants (Table 2.1: male infants, 3096.2 g (Never-smokers: NS) vs. 2959.8 g (Current smokers: SM) [$p < 0.001$]; female infants, 3018.2 g (NS) vs. 2893.7 g (SM) [$p < 0.001$]) [34]. This study provides valuable evidence to support the importance of cessation of maternal smoking before and during pregnancy.

Next, although it has been suggested that severe nausea and vomiting in early pregnancy (NVP) and hyperemesis gravidarum (HG), which is an extreme form of NVP, were associated with weight loss, there is no clear consensus on the association HG and NVP and fetal growth. Thus, Morokuma et al. examined the association between HG and NVP and small-for-gestational-age (SGA) using data of JECS [35]. As a result, the risk ratios of SGA birth (95% confidence interval) for mothers with severe NVP and those with HG were 0.86 (0.62–1.19) and 0.81 (0.39–1.66), respectively [35]. The results suggested that neither severe NVP nor HG was associated with increased risk for SGA birth.

In conclusion, regarding DOHaD, it is important to estimate fetal environment including environmental and maternal lifestyle factors and its effects on fetal and childhood growth and development. Although JECS is relatively new study, there is some strength as a nationwide birth cohort study. In the future, a lot of valuable findings which might contribute to describe and clarify the mechanism of DOHaD could be developed.

2.5 An Example of the Study Using Birth Registration Data (Vital Statistics): Effects of the Great East Japan Earthquake on Secondary Sex Ratio (SSR) and Perinatal Outcomes

2.5.1 Birth Registration Data (Vital Statistics)

In Japan, every birth must be registered by law. These data were anonymously provided under the Statistics Act in Japan. These data contain the birthplace, birth date, sex of children, birth weight, gestational age, parity, and ages of the father and mother. Except for the ages of the parents, the obstetrician who attended the birth provided this information on the birth certificate. It was not compulsory to obtain permission to use their birth registration data in the study from the participants because it is available for researchers to use the birth registration data with permission from the Ministry of Health, Labour and Welfare under the Statistics Act in Japan.

Table 2.1 Crude and Adjusted mean birth weight in male and female infants without preterm birth (original data: Suzuki et al., 2016 [34])

Smoking status during early pregnancy	Male					Female				
	Crude mean birth weight (g)	Standard error	Adjusted mean birth weight (g)[a]	Standard error	*p*-value[b]	Crude mean birth weight (g)	Standard error	Adjusted mean birth weight (g)[a]	Standard error	*p*-value[b]
Never-smokers (NS)	3102.6	8.3	3141.8	17.5		3007.7	8.2	3055.5	16.4	
Ex-smokers who quit before pregancy (QSB)	3110.6	12.1	3133.8	19.2	0.9	3031.6	12.3	3069.2	18.2	0.6
Ex-smokers who quit during early pregnancy (QSD)	3116.9	15.5	3109.7	21.0	0.2	2999.7	16.8	3021.1	20.7	0.14
Current smokers (SM)	2994.1	26.3	3004.6	28.4	<0.001	2875.2	24.7	2928.0	28.2	<0.001

[a]Adjusted for partners' smoking status, annual household income, birth order of children, PIH, DM/GDM, maternal weight before pregnancy, maternal weight gain during pregnancy, maternal age group at delivery and gestational duration calculated by least squares mean adjustment
[b]*p*-value was calculated using Dunnett's test by least squares mean adjustment

2.5.2 The Study Using Birth Registration Data Related to DOHaD

The effect of natural disasters such as earthquake on perinatal outcomes has been previously examined. However, previous studies had certain limitations. For example, although an effect of seasonality may be noted for SSR [36–38] or preterm births [39], none of the above studies strictly adjusted for seasonal changes in perinatal outcomes. Furthermore, when individual data was used for analysis, the sample size of the study was relatively small, while when the number of subjects was large, these studies were designed as ecological studies. Thus, it might be difficult to conclude the causal association between natural disasters and perinatal outcomes. On 11 March 2011, a huge earthquake occurred in East Japan, called the Great East Japan Earthquake. Subsequently, a massive tsunami struck the area, and millions of people were affected by this earthquake and tsunami. This earthquake was determined to be the most severe natural disaster in Japan in recorded history [40]. We examined the effects of the Great East Japan Earthquake on SSR, birth weight, and gestational duration in weeks using individual birth registration data in the most severely affected prefectures and other prefectures in Japan [41].

Individual birth registration data from the vital statistics of Japan between March 2010 and March 2012 were used for this study [41]. To examine the effect of the earthquake on SSR and perinatal outcomes, we compared the following two groups. Pregnant women who experienced the earthquake at 4–36 weeks of gestation were categorized according to their gestational period as of 11 March 2011, as follows: gestational weeks 4–11, 12–19, 20–27, and 28–36 (2011 group, $n = 679{,}131$) [41]. Similarly, pregnant women who did not experience the earthquake were categorized according to their gestational period as of 11 March 2010 and used as controls (2010 group, $n = 688{,}479$) [41].

As a result, in the extremely affected region, the SSR among women at 4–11 weeks of gestation significantly declined in the 2011 group as compared with the 2010 group (Table 2.2: 49.8% vs. 52.1%, $p = 0.009$) [41]. In the extremely affected region, women who experienced the earthquake at 28–36 weeks of gestation were likely to deliver infants with significantly lower birth weights [41]. These results suggested that the SSR declined among women who experienced the earthquake during early pregnancy, particularly in the extremely affected region. However, no apparent negative effect of the earthquake on perinatal outcomes was observed.

From the view of public health, the effect of disaster on perinatal and childhood outcomes might be important. In addition, regarding DOHaD, this kind of large disaster might be an important factor which is associated with fetal and early childhood environment. Therefore, it is important to examine the effect of some environmental factors like disaster on birth outcomes by using the public data like vital statistics.

Table 2.2 Comparison of secondary sex ratio (SSR) of all singleton babies between 2010 group and 2011 group in each gestational period category and region (original data: Suzuki et al., 2016 [41])

Gestational weeks	4–11 weeks			12–19 weeks			20–27 weeks			28–36 weeks		
	Total	Male	*p**	Total	Male	*p*	Total	Male	*p*	Total	Male	*p*
Extremely affected region												
2010 group	6798	3541 52.1	0.009	7082	3680 52.0	0.66	6948	3499 50.4	0.07	7518	3863 51.4	0.07
2011 group	6618	3298 49.8		6716	3465 51.6		6649	3450 51.9		7223	3604 49.9	
Moderately affected region												
2010 group	66,757	34,155 51.2	0.97	65,525	33,949 51.8	0.86	65,018	33,251 51.1	0.28	68,824	35,380 51.4	0.61
2011 group	65,137	33,320 51.2		64,947	33,617 51.8		63,721	32,780 51.4		67,872	34,798 51.3	
Slightly or unaffected region												
2010 group	94,792	48,980 51.7	0.0011	94,700	48,466 51.2	0.43	92,986	48,127 51.8	0.21	99,176	51,149 51.6	0.48
2011 group	93,363	47,541 50.9		94,709	48,641 51.4		91,825	47,257 51.5		98,359	50,573 51.4	

**p values were calculated by Chi-square test*

2.6 Conclusion

In Japan, there are some population-based birth cohort studies, and these studies established the findings related to DOHaD. These population-based DOHaD evidences could directly apply to public health activity not only in local community but also nationwide level. In addition, some previous findings might be valuable to clarify the mechanisms of DOHaD although some epidemiological limitations existed. In the future, it is expected that a lot of scientific evidences will be produced from these cohort studies.

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