The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2020; 27: 204-214. http://doi.org/10.5551/jat.49577

The Perinatal Condition Around Birth and Cardiovascular Risk Factors in the Japanese General Population: The Suita Study

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Aim: To investigate the relationship between perinatal condition around birth and cardiovascular risk in later life.

Methods: Retrospective data were examined from 1241 city dwellers (521 men, 720 women; age 41–69 years) who had undergone medical examination at a single institution including blood tests and physical measurements from 2007 to 2008. The questionnaire was conducted to determine how perinatal factors affect their lives later. We also selected and studied a total of 28 individuals (12 men and 16 women) specifically about the conformity rate of the breastfeeding method between participants' memories and what was written in the maternal and child health handbooks.

Results: The conformity rate of the breastfeeding method between a self-questionnaire and his/her maternal and child health handbook was well correlated ($r = 0.73$; $p < 0.025$). Among the data in women who were born at home, HbA1C levels (5.36 ± 0.03 vs. 5.25 ± 0.05 mg/dL, $p = 0.03$) and low-density lipoprotein cholesterol (136.0 ± 1.4 vs. 129.3 ± 2.5 mg/dL, $p = 0.04$) were higher than women who were born at the hospital. Women raised by formula showed higher low-density lipoprotein cholesterol levels than women fed breast milk or a mixture of breast milk and formula (150.2 ± 4.8 vs. 138.7 ± 3.7, 142.5 ± 2.6 mg/dL, $p = 0.04$). Fasting blood glucose levels at an adult time in men and women born through breech presentation were higher than those by the cephalic presentation (123.2 ± 7.8 vs. 106.8 ± 1.2 mg/dL, $p = 0.03$).

Conclusion: The study proposed that some perinatal conditions around birth such as delivery place, presenting part, and lactation affected especially Japanese women's cardiovascular risks between ages 41 and 69 years.

See editorial vol. 27: 199-200

Key words: Cardiovascular risk, Delivery, Perinatal condition, Lactation

Introduction

A key question in development is whether the early environment influences long-term health or achievement. Data from small mammals and primates show that early nutrition may have a potentially crucial long-term effect, e.g., on blood liquids, plasma insulin, obesity, atherosclerosis, behavior, and learning[1]. Perinatal conditions influencing the cardiovascular diseases in adulthood include during the periconceptional, fetal, and infant phases of life. Research in evolutionary biology, developmental biology, and animal and human physiology has provided support for this idea[2, 3]. Initially, genetic factors may mostly influence fetal development and growth. However, when development is inhibited by maternal constraint (physics, size of the pelvis, nutritional status, primiparous, placental function) a PARs (predictive adaptive

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Received: March 26, 2019 Accepted for publication: June 9, 2019

response) can occur even in the absence of severe uterine environmental degradation[2, 3].

After World War II, Japanese socioeconomic status including the food and nutrition situation had dramatically changed. Even though Japan was in the process of changes from the agrarian to the industrial society, the food and nutrition situation was better at that time; however, the maternal constraints were not changed under the circumstance as explained above. The inappropriate PARs occurred in utero shortly after birth no matter what the food and nutrition status was in Japan. Some Japanese researchers have described the relationship between birthweight and lifestyle diseases during that time[4]. Also, some reports indicated the close relationship between the conditions at birth and cardiovascular risks later in life[5, 6]. However, few studies have shown how the place of birth, presenting part, and delivery mode affect the cardiovascular risk in later life. We aimed to analyze the data in this study and focused on precisely the connection of the perinatal conditions around birth such as delivery mode, delivery place, presenting part and lactation, and cardiovascular risks later in life.

Methods

Participants

We examined blood tests and physical measurements from a total of 1241 Japanese living in the urban area (521 men and 720 women aged between 41 and 69 years) from the Suita Study[7-9]. It was held at the Department of Preventive Cardiology of the National Cardiovascular Center (currently, National Cerebral and Cardiovascular Center) from January 2007 to June 2008. Blood samples were collected after the participants had fasted for at least 10 h. The samples were immediately centrifuged, and a routine blood examination that included serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, and glucose levels were performed. Value for HbA_{1C} (%) was estimated as the National Glycohemoglobin Standardization Program equivalent value (%) calculated by the following formula: HbA_{1C} (%) $= 1.02 \times HbA_{1C}$ (Japan Diabetes Society, %) + 0.25%[10]. Blood pressure was measured by a standard sphygmomanometer (OMRON, BP-103i). After the participants had been in a seated position for 5 min, blood pressure was measured twice on the right arm, and the average of the two measurements was used in the analyses.

On the same day after physical measurements and blood tests, we conducted a questionnaire survey including the conditions around birth that were categorized into four parts: 1) delivery mode, 2) delivery place, 3) presenting part, and 4) lactation. Those who answered "did not remember" on the questionnaire were excluded from future evaluation. Well-trained nurses obtained information on cigarette smoking status (current-smoker, ex-smoker, or non-smoker), alcohol drinking status (current-drinker, ex-drinker, or non-drinker), and medical histories[7-9].

We requested participants to submit their maternal and child health handbooks and then the conformity rate of the breastfeeding method between what they remembered they were fed and what they were actually fed written in the maternal and child health handbook such as breast milk, mixed, or formula.

We investigated the relationships between conditions around birth (delivery mode, delivery place, presenting part, and lactation) and cardiovascular risk factors in later life. The participants were initially divided by their sex. The respective groups' values were then adjusted based on age, body mass index (BMI), medication (antihypertensives, antidiabetics, and hyperlipidemia agents), and lifestyle (current smoking, current alcohol drinking). We adjusted for the number of sex in each group when we performed sex-combined analysis.

Statistical Analysis

For continuous variables, Student *t* test was performed for the analysis of the normally distributed data; otherwise, a Wilcoxon test was used. We used analysis of variance when evaluating the respective group data. To compare the groups, we used analysis of variance and covariance is age, BMI, and medication (antihypertensives, antidiabetics, hyperlipidemia agents). All statistical analyses were performed to using Statistical Package for Social Science software program (Windows version 20.0J; Chicago, IL, USA). We defined p value < 0.05 as significant difference.

Ethics Statement

This study was approved by the institutional research ethics committee of the National Cerebral and Cardiovascular Center, Osaka, and was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Results

We studied 1241 participants (521 men and 720 women). The median (range) age of the participants was 61 (41–69) years for men and 59 (41–69) years for women. The population characteristics are shown in **Table 1** and participant flow chart is shown in **Fig. 1**. The number of final participants for each query

Table 1. Population characteristics

	Men (n = 521)	Women (n = 720)
Age, median (range)	61 (41-69)	59 (41-69)
41-50 y, 51-60 y, 61-69 y	68, 191, 262	98, 309, 313
Systolic BP (mmHg)	126.8 ± 0.8	120.7 ± 0.7
Diastolic BP (mmHg)	81.1 ± 0.5	74.0 ± 0.4
Pulse rate (bpm)	68.7 ± 0.7	67.7 ± 1.1
Waist circumference (cm)	85.3 ± 0.4	80.2 ± 0.4
BMI (m/kg^2)	23.7 ± 0.1	22.2 ± 0.1
T-C (mg/dL)	200.3 ± 1.7	217 ± 2.9
Triglyceride (mg/dL)	125.0 ± 4.3	90.9 ± 1.7
HDL- C (mg/dL)	56.5 ± 0.7	67.7 ± 0.6
LDL- C (mg/dL)	118.8 ± 1.7	131.6 ± 2.8
Glucose (mg/dL)	107.6 ± 1.4	97.5 ± 0.5
HbA1C (%)	5.47 ± 0.05	5.40 ± 0.08
Current smoking, n (%)	149 (28.6)	51 (7.1)
Current drinking, n (%)	362 (69.5)	222 (30.8)

Age is shown as median (range). Other data are shown as mean ± SD. BMI, body mass index; BP, blood pressure; T-C, total cholesterol; HDL-C, high-density.

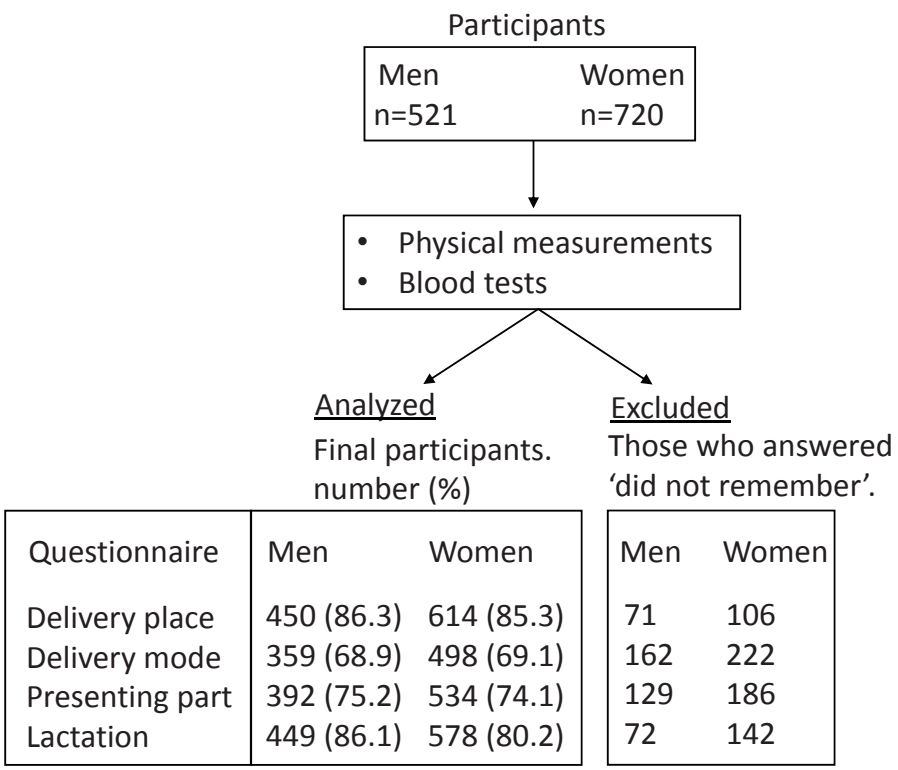

Fig. 1. Participant flow chart

The number of participants was 521 men and 720 women. In the questionnaire survey, those who answered "did not remember" were excluded from the study.

is shown in Fig. 1. There was no correlation among these factors including place of the delivery, breast-feeding method, and presenting position.

Conformity between the Self-Reported and Actual Way of Breastfeeding Method

Twenty-eight participants (12 men and 16

women) were examined and able to provide their maternal and child health handbooks. The 28 people accurately extracted from their memories what they were fed including breast milk, mixed, or formula. Their memories were confirmed with their maternal and child health handbooks, and the conformity rate was 0.731. When we formed a hypothesis that the conformity rate of the confidence interval and the conformity rate were supposed to be zero, the 95% confidence intervals (95% CI) should be between 0.0451 and 0.886 ($p=0.03$). Therefore, it could be explained that the relationship between the participants' memories and what was written in the maternal and child health handbook was highly matched and reliable[4].

Delivery Place

Four hundred fifty men answered that they remembered their delivery place. Three hundred and eleven (69.1%) were born at home, and 139 (31.9%) were delivered at a hospital (**Table 2a**). We could not find any differences in cardiovascular risks for those groups. On the other hand, 614 women answered the same question, and 433 (70.5%) were delivered at home. In addition, the hospital was a choice to be born for 181 (29.5%) women (**Table 2b**). It was interesting to see that women born at home had significantly higher HbA1C (5.36 ± 0.03 vs. 5.25 ± 0.05%, $p=0.03$) and LDL-C (135.0 ± 4.1 vs. 130.3 ± 2.5 mg/dL, $p=0.04$) than those who were born at the hospital.

Presenting Part

A total of 857 men and women responded to the question about their presenting part at delivery (**Table 3**). Eight hundred and thirty (96.9%) were born through cephalic presentation. Therefore, the population of the breech presentation was very small in number, which was only 27 (3.1%), and that made it difficult to evaluate by sex. However, fasting blood glucose level was higher in breech presentation than in cephalic presentation (123.2 ± 7.8 vs. 106.8 ± 1.2 mg/dL, $p=0.03$).

Delivery Mode

Nine hundred and twenty-six men and women acknowledged their delivery mode. Nine hundred and sixteen (98.9%) were born vaginally, and the rest of the people, 10 (1.1%), were born by cesarean section (**Table 4**). The query was too small to evaluate by sex. There were no differences in cardiovascular risks between those delivery modes.

Lactation

Four hundred and forty-nine men responded and answered the question related to the feeding type. Three hundred and thirty-one (73.7%) were raised with breast milk, 75 (16.7%) were fed with a mixture of breast milk and formula, and 43 (9.6%) men were given formula only. There were no cardiovascular risks associated with the different types of feeding (**Table 5a**). Meanwhile, 578 women responded as well. Four hundred and twenty (72.7%) women had their breast milk, and 105 (18.2%) were fed with the mixture of breast milk and formula. Moreover, 53 (9.2%) women were fed with formula (**Table 5b**). Women raised by formula indicated higher total cholesterol levels than those women fed breast milk or mixture of breast milk and formula (233 ± 5.3 vs. 226.7 ± 2.8 and 222 ± 4.1 mg/dL, $p=0.07$). LDL-C was higher in the formula feeding than the other two types (breast milk and mixture) of feeding (150.2 ± 5.3 vs. 138.7 ± 3.7 and 142.5 ± 2.6 mg/dL, $p=0.04$).

Discussion

In this study, we investigated whether conditions at the perinatal and infantile period would relate to future cardiovascular risks. The study showed that either women who were born at home or raised by formula tended to have dyslipidemia. Moreover, women who were born through breech presentation tended to have an increase in fasting glucose level.

Historical Background

It is important to be aware that participants in this study were born between 1939 and 1968 (average: 1948), since the time they were born was in the transition of the economic growth after the World War II. In addition, not only the food supply was impoverished but also the neonatal mortality rate in the 1950s was 20–30 times higher than in 2017. While the participants currently live in cities, the food supply would have been poor throughout Japan around the time they were born. Thus, it is possible that their mothers would have experienced maternal malnutrition and most of the participants could have been undernourished during both fetal and infant periods like Fiege of Leningrad, which lasted 3 years. It is supposed that these effects of malnutrition and low socioeconomical status would be generally stronger when the participants had older age.

Home Delivery and Malnutrition in Fetal and Infant Periods

In Japan, those born at home were significantly decreased from the 1950s to 1970s. In the early

Table 2a. Risk characteristics and delivery place

	Delivery place			
Men ($n=521$)	Home	Hospital	Unknown	*P* values
Number (%)	311 (59.6)	139 (26.6)	71 (13.6)	
Age, median (interquartile range)	62 (51-67)	59 (48-64)	61 (49-67)	
Systolic BP (mmHg)	126.8 ± 1.0	126.8 ± 1.7	126.9 ± 1.9	0.97
Diastolic BP (mmHg)	80.7 ± 0.6	81.6 ± 1.0	81.0 ± 1.2	0.47
Pulse rate (bpm)	68.7 ± 0.7	67.7 ± 1.1	68.1 ± 1.3	0.81
Waist circumference (cm)	85.7 ± 0.3	85.9 ± 0.4	85.8 ± 0.7	0.76
BMI (m/kg^2)	23.5 ± 0.4	23.5 ± 0.6	23.6 ± 0.8	0.71
T-C (mg/dL)	200.3 ± 1.7	202.3 ± 2.9	201.0 ± 3.2	0.56
Triglyceride (mg/dL)	126.7 ± 5.8	132.7 ± 9.7	127.8 ± 11.0	0.57
HDL- C (mg/dL)	56.2 ± 0.7	55.4 ± 1.4	55.8 ± 1.7	0.60
LDL- C (mg/dL)	118.8 ± 1.7	120.4 ± 2.8	119.2 ± 3.0	0.64
Glucose (mg/dL)	107.6 ± 1.4	106.1 ± 2.4	106.8 ± 2.6	0.59
HbA1C (%)	5.47 ± 0.05	5.40 ± 0.08	5.45 ± 0.09	0.46
Current smoking, *n* (%)	86, (16.3)	40, (7.6)	23, (4.4)	0.95
Current drinking, *n* (%)	210, (40.3)	94, (18.0)	58, (11.1)	0.93

Adjusted for age, BMI, life style (current smoking, current drinking), medication (antihypertensives, antidiabetics, hyperlipidemia agents). BMI was adjusted for life style and medication. Age is shown as median (interquartile range). Other data are shown as mean ± SD. BMI, body mass index; BP, blood pressure; T-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2b. Risk characteristics and delivery place

	Delivery place			
Women ($n=720$)	Home	Hospital	Unknown	
Number (%)	433 (60.1)	181 (25.1)	106 (14.7)	*P* values
Age, median (interquartile range)	62 (51-66)	59 (48-63)	61 (49-66)	
Systolic BP (mmHg)	120.9 ± 0.8	119.4 ± 1.4	119.9 ± 1.7	0.38
Diastolic BP (mmHg)	74.1 ± 0.5	73.3 ± 0.9	73.6 ± 1.2	0.48
Pulse rate (bpm)	68.4 ± 0.4	69.1 ± 0.79	68.7 ± 0.85	0.46
Waist circumference (cm)	79.7 ± 0.3	79.7 ± 0.5	79.9 ± 0.7	0.99
BMI (m/kg^2)	22.2 ± 0.3	22.1 ± 0.5	22.2 ± 0.7	0.91
T-C (mg/dL)	220.8 ± 1.5	217.1 ± 2.7	218.6 ± 3.0	0.20
Triglyceride (mg/dL)	93.4 ± 2.1	86.7 ± 3.9	89.2 ± 4.2	0.14
HDL- C (mg/dL)	67.1 ± 0.7	69.5 ± 1.2	68.5 ± 1.4	0.08
LDL- C (mg/dL)	136.0 ± 1.4	129.3 ± 2.5	134.2 ± 2.9	0.04※
Glucose (mg/dL)	97.8 ± 0.6	96.0 ± 1.1	96.8 ± 1.3	0.10
HbA1C (%)	5.36 ± 0.03	5.25 ± 0.05	5.30 ± 0.06	0.03※
Current smoking, *n* (%)	30, (4.0)	13, (1.0)	8 (1.0)	0.86
Current drinking, *n* (%)	133, (18.4)	56, (7.7)	33 (4.5)	0.87

Adjusted for age, BMI, life style (current smoking, current drinking), medication (antihypertensives, antidiabetics, hyperlipidemia agents). BMI was adjusted for life style and medication. Age is shown as median (interquartile range). Other data are shown as mean ± SD. BMI, body mass index; BP, blood pressure; T-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; One asterisk means $P<0.05$.

1950s, those born in a hospital is only 5%; however, in 1970s, 96% of the newborn was born in a hospital[11]. In the current study, most of the participants were born and grew up around 1940s and 1950s. Therefore, the significant associations are possibly associated with this change. Seventy percent of participants in this study were born at home around 1945, and they might belong to a low-income family and also born and grew up in low socioeconomic status. Olsuanya *et al.* compared 918 severely undernourished

Table 3. Risk characteristics and presenting part

	Presenting part			
Men, Women (n = 1241)	Cephalic presentation	Breech presentation	Unknown	P values
Number (%)	830 (66.8)	27 (2.1)	384 (30.9)	
Age, median (interquartile range)	60 (50-66)	60 (49-66)	60 (49-66)	
Systolic BP (mmHg)	126.7 ± 0.9	129.4 ± 5.6	127.9 ± 1.2	0.63
Diastolic BP (mmHg)	81.0 ± 0.5	83.0 ± 3.3	82.1 ± 0.7	0.56
Pulse rate (bpm)	67.5 ± 0.5	67.8 ± 3.5	67.7 ± 0.7	0.92
Waist circumference (cm)	82.1 ± 0.2	82.4 ± 0.9	82.3 ± 0.4	0.74
BMI (m/kg^2)	22.9 ± 0.3	23.0 ± 0.6	23.0 ± 0.6	0.68
T-C (mg/dL)	201.1 ± 1.4	197.5 ± 9.2	200.2 ± 1.8	0.69
Triglyceride (mg/dL)	128.9 ± 5.0	152.5 ± 15.2	145 ± 6.1	0.46
HDL- C (mg/dL)	56.0 ± 0.7	51.3 ± 4.5	53.0 ± 1.0	0.30
LDL- C (mg/dL)	119.3 ± 1.4	115.6 ± 9.1	117.2 ± 2.1	0.68
Glucose (mg/dL)	106.8 ± 1.2	123.2 ± 7.8	109.5 ± 1.8	0.03※
HbA1C (%)	5.45 ± 0.04	5.71 ± 0.29	5.50 ± 0.08	0.37
Current smoking, n (%)	132, (10.6)	5, (0.4)	62, (4.9)	0.87
Current drinking, n (%)	390, (31.4)	13, (1.0)	181, (14.6)	0.90

Adjusted for age, BMI, life style (drinking, smoking, exercise), medication (antihypertensives, antidiabetics, hyperlipidemia agents, and sex. BMI was adjusted for life style, medication, and sex. Age is shown as median (interquartile range). Other data are shown as mean ± SD. BMI, body mass index; BP, blood pressure; T-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; One asterisk means $P < 0.05$.

Table 4. Risk characteristics and delivery mode

	Delivery mode			
Men, Women (n = 1241)	Vaginal delivery	Cesarean section	Unknown	P values
Number (%)	916 (73.8)	10 (8.0)	315 (25.3)	
Age, median (interquartile range)	60 (50-66)	57 (47-63)	60 (49-66)	
Systolic BP (mmHg)	127.0 ± 0.8	133.2 ± 7.9	130.2 ± 1.6	0.43
Diastolic BP (mmHg)	81.2 ± 0.5	83.5 ± 4.7	83.2 ± 0.9	0.62
Pulse rate (bpm)	67.8 ± 0.5	73.4 ± 5.1	72.4 ± 0.9	0.26
Waist circumference (cm)	82.2 ± 0.2	80.8 ± 1.5	81.2 ± 0.6	0.33
BMI (m/kg^2)	22.9 ± 0.3	23.0 ± 0.6	22.9 ± 0.4	0.38
T-C (mg/dL)	201.2 ± 1.4	211.7 ± 8.4	208.5 ± 2.6	0.44
Triglyceride (mg/dL)	126.7 ± 4.5	106.4 ± 24.0	114.5 ± 6.4	0.64
HDL- C (mg/dL)	56.4 ± 0.7	60.1 ± 6.4	58.5 ± 1.3	0.56
LDL- C (mg/dL)	119.5 ± 1.3	130.3 ± 7.9	125.6 ± 3.5	0.40
Glucose (mg/dL)	106.9 ± 1.1	115.0 ± 8.7	109.5 ± 2.5	0.45
HbA1C (%)	5.43 ± 0.04	5.87 ± 0.40	5.56 ± 0.12	0.27
Current smoking, n (%)	146, (11.8)	16, (1.3)	37, (3.0)	0.87
Current drinking, n (%)	430, (34.6)	47, (3.8)	107, (8.6)	0.91

Adjusted for age, BMI, life style (current smoking, current drinking), medication (antihypertensives, antidiabetics, hyperlipidemia agents). BMI was adjusted for life style and medication. Age is shown as median (interquartile range). Other data are shown as mean ± SD. BMI, body mass index; BP, blood pressure; T-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

infants with 1836 controls in a low-income urban population; infants delivered at residential homes had a two-three-fold greater likelihood of being severely underweight[12]. The study demonstrated that delivery in homes is a potential marker for severe undernutrition in early infancy in urban populations in low-income countries[12]. It would be very reasonable if the same theory is applied in this current study. Because maternal malnutrition is proved to be highly related to intrauterine growth restriction and prenatal and post-

Table 5a. Risk characteristics and lactation

	Lactation				
Men ($n=521$)	Breast milk	Mixed	Formula	Unknown	*P* values
Number (%)	331 (63.5)	75 (14.4)	43 (8.3)	72 (13.8)	
Age, median (interquartile range)	60 (50-66)	59 (49-66)	58 (49-66)	59 (50-66)	
Systolic BP (mmHg)	127.0 ± 0.9	119.4 ± 1.4	128.1 ± 4.3	127.1 ± 1.4	0.58
Diastolic BP (mmHg)	81.2 ± 0.5	73.3 ± 0.9	80.3 ± 2.6	79.5 ± 1.0	0.76
Pulse rate (bpm)	67.8 ± 0.6	69.1 ± 0.79	64.6 ± 2.8	68.2 ± 0.80	0.53
Waist circumference (cm)	79.5 ± 0.5	79.7 ± 0.5	81.2 ± 1.1	79.8 ± 0.5	0.82
BMI (m/kg^2)	23.5 ± 0.3	23.5 ± 0.6	23.6 ± 0.8	23.6 ± 0.6	0.83
T-C (mg/dL)	199.7 ± 1.5	217.1 ± 2.7	195.3 ± 7.4	201.5 ± 2.7	0.37
Triglyceride (mg/dL)	127.2 ± 5.0	86.7 ± 3.9	116.7 ± 9.8	115.3 ± 4.2	0.81
HDL- C (mg/dL)	55.5 ± 0.7	69.5 ± 1.2	57.9 ± 3.4	67.2 ± 1.3	0.33
LDL- C (mg/dL)	118.8 ± 1.4	130.3 ± 2.5	114.1 ± 7.2	116.2 ± 2.5	0.38
Glucose (mg/dL)	106.7 ± 1.2	96.0 ± 1.1	109.9 ± 6.1	104.7 ± 1.5	0.47
HbA1C (%)	5.44 ± 0.05	5.25 ± 0.05	5.61 ± 0.23	5.42 ± 0.07	0.32
Current smoking, *n* (%)	95, (18.2)	22, (4.2)	13, (2.3)	26, (5.0)	0.88
Current drinking, *n* (%)	230, (44.1)	52, (10.0)	30, (5.8)	50, (9.6)	0.88

Adjusted for age, BMI, life style (current smoking, current drinking), medication (antihypertensives, antidiabetics, hyperlipidemia agents). BMI was adjusted for life style and medication. Age is shown as median (interquartile range). Other data are shown as mean ± SD. BMI, body mass index; BP, blood pressure; T-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 5b. Risk characteristics and lactation

	Lactation				
Women ($n=720$)	Breast milk	Mixed	Formula	Unknown	
Number (%)	420 (58.3)	105 (18.2)	53 (9.2)	142 (19.7)	*P* values
Age, median (interquartile range)	60 (50-66)	59 (49-66)	58 (49-66)	59 (50-66)	
Systolic BP (mmHg)	119.1 ± 1.5	119.5 ± 2.2	118.8 ± 2.8	118.9 ± 2.1	0.96
Diastolic BP (mmHg)	72.6 ± 0.93	73.4 ± 1.3	71.8 ± 1.8	72.9 ± 1.2	0.66
Pulse rate (bpm)	70.3 ± 0.8	70.9 ± 1.2	70.3 ± 1.6	70.4 ± 1.1	0.82
Waist circumference (cm)	79.2 ± 0.5	79.4 ± 0.7	78.7 ± 0.9	79.0 ± 0.6	0.72
BMI (m/kg^2)	22.2 ± 0.3	22.1 ± 0.5	22.3 ± 0.7	22.2 ± 0.6	0.91
T-C (mg/dL)	222.7 ± 4.1	226.8 ± 2.8	233.6 ± 5.3	230.2 ± 2.9	0.07
Triglyceride (mg/dL)	88.9 ± 4.0	90.0 ± 5.7	93.1 ± 7.4	91.2 ± 5.6	0.81
HDL- C (mg/dL)	66.6 ± 1.3	66.6 ± 1.8	64.8 ± 2.4	66.2 ± 1.7	0.39
LDL- C (mg/dL)	138.7 ± 3.7	142.5 ± 2.6	150.2 ± 4.8	143.7 ± 2.5	0.04※
Glucose (mg/dL)	94.5 ± 1.0	95.5 ± 1.4	92.4 ± 1.8	94.5 ± 1.4	0.24
HbA1C (%)	5.30 ± 0.04	5.30 ± 0.05	5.30 ± 0.07	5.30 ± 0.05	0.98
Current smoking, *n* (%)	30, (4.2)	10, (1.4)	5, (0.7)	6, (0.8)	0.75
Current drinking, *n* (%)	129, (17.9)	40, (5.5)	21, (1.7)	32, (4.4)	0.81

Adjusted for age, BMI, life style (current smoking, current drinking), medication (antihypertensives, antidiabetics, hyperlipidemia agents). BMI was adjusted for life style and medication. Age is shown as median (interquartile range). Other data are shown as mean ± SD. BMI, body mass index; BP, blood pressure; T-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

natal malnutrition, it induces abnormalities such as obesity and changes in endocrine system[13-16]. We have also shown that moderate maternal food restriction in mice impairs physical growth, behavior, and neurodevelopment of offspring[17]. The current study indicated that people who were born at home, which is interpreted as their mother might have been undernourished during pregnancy, especially in women, had cardiovascular risks, such as high HbA1C, high LDL-C, and low HDL-C in later life. Maternal malnutrition and undernourishment in infancy might have led to a decrease in adult β-cell function, which is a crucial

component in the development of type 2 diabetes[18]. Most human organ systems begin to develop early in gestation and do not become fully mature in anatomy and function until weeks, months, or years after birth[19, 20]. Extensive human epidemiologic and animal model data indicate that during critical periods of prenatal and postnatal mammalian development, nutrition and other environmental stimuli influence developmental pathways and thereby induce permanent changes in metabolism and chronic disease susceptibility[21]. It supported that fetal and infant nutrition status was deeply connected with obesity and led to high HbA1C and hyperlipidemia later in life among female participants in the study. Barker *et al.* reported that malnutrition at fetal and infant period lead to future obesity, diabetes mellitus, hyperlipidemia, hypertension, and increases the mortality by cardiovascular diseases[22].

Breech Presentation and Future Development of Glucose Intolerance

The breech presentation occurred in 3.1% of all pregnancies in our study, which was an acceptable range or slightly lower than the latest report. It could be related that vaginal breech delivery is associated with neonatal mortality and morbidity rate that is four times higher than cesarean delivery[23-25]. As the study presented, babies born by breech presentation had higher fasting glucose level than those born by cephalic presentation. According to Cui at al., common determinants of breech presentation are maternal gestational diabetes mellitus[26], as well as low gestational age, advanced maternal age, a scarred uterus, or congenital malformation of the fetus[27, 28]. It is possible that the breech presentation causes risks for fetal demise as follows: the insult is not acute hypoxic-ischemic stress related not only to delivery alone but also to persistent hypoxic-ischemic stress in utero which consequently leads to dysfunction of organs and insufficient secretion of insulin, insulin resistance, and ultimately to future glucose intolerance[28]. It is essential to understand that genetic factors might also have been involved with the future development of glucose intolerance[26], although as we discussed, perinatal conditions have a significant impact on the future development of glucose intolerance.

Formula-Fed and Future Hyperlipidemia

Percentages of breast milk were significantly decreased from 70.5% to 31.7% from the 1960s to 1970s[29]. It is reasonable that those who were brought up with breast milk had higher ages than those who were brought up with other lactation methods. However, those who were brought up with breast milk had lower cardiovascular risks than other groups; this association seems to be in the opposite direction from "delivery places" in terms of a cohort effect.

In the systematic review of the effect of breastfeeding in infancy on blood pressure in later life, the pooled mean difference in systolic blood pressure was −1.10 mmHg (95% confidence interval −1.79 to −0.42 mmHg) in comparison to formula fed in later life, but with significant heterogeneity[30]. Until the 1980s, the sodium content of breast milk in Western countries was much lower than that of formula milk[31, 32]. Long-chain polyunsaturated fatty acids are present in breast milk but not in formula milk. These play an important part in the vascular endothelium and, when given as nutritional supplements, seem to affect blood pressure and lipid metabolism[31, 32]. Reports from histological cohort studies suggest that blood cholesterol in adulthood may be influenced by infant feeding, while formula-fed has been related to higher level of adult serum cholesterol[33, 34]. Interestingly, mean total cholesterol in childhood and adolescence showed no consistent difference between those breastfed and formula-fed in early life. However, in adults, mean total cholesterol was lower in those who were breastfed. Although the overall difference was modest, it was remarkably consistent between studies[35]. When discussing the relationship between formula-fed and hyperlipidemia, the current research clearly explained that people who were fed by formula had higher numbers of total and LDL-C than the other groups. In addition, slower weight gain is observed in breastfed compared with formula-fed babies[34]. Singhal and Lucas proposed the growth acceleration hypothesis that more rapid infant growth results in increased risk of later development of cardiovascular disease and obesity[36]. Subsequently, there have been reports from both observational studies and randomized trials that are consistent with the hypothesis that more rapid early growth caused by formula-fed is causally related to adverse effects on the later development of glucose intolerance[37], hypertension[34], hyperlipidemia[33, 38], and risk of obesity[34]. As far as we reviewed the data in our study, the ratio of breast milk related to decreased total and LDL-C level in later life. Moreover, it has been reported that these effects are more significant when one takes breast milk for a more extended period[39]. Singhal *et al.* quantified the precise volume of early human milk and formula intake and showed prospectively that increased consumption of human milk was associated with reduced ratios of LDL to HDL cholesterol later in life[35].

In this study, 7% of women smoked and 31% consumed alcohol, which was less than half than that in men[4]. In Japan, women's BMI decreased from 23.2

to 22.5 kg/m^2, indicating that women's tendency toward thinness prevailed over the past 30 years (1980–2010)[40]. The men in their 50s were the age group that their BMI increased from 22.6 to 24.1 over the 30 years (1980–2010)[40]. The incident of metabolic syndrome in men was 2 to 4 times higher than women[40]. Therefore, women have healthy lifestyle including less smoking and less consuming of alcohol, compared to men in general. It can be considered that epigenetics also affects the occurrence of hyperlipidemia and diabetes mellitus in later life.

The Study Strengths and Limitations

The strength of this study is the high reliability of the data as the blood samples were uniformly measured in a standardized manner, and physical, and blood pressure measurements were done by well-trained nurses in the stable conditions. In this study, we used a questionnaire as a recall of the presentation part at delivery and delivery mode, and there is the possibility of recall bias. However, in the previous study, the relationship between the participants' memories of birthweight and what was written in the maternal and child health handbook was highly matched[4], and also in the current study, the participants' memories about lactation and what was written in the maternal and child health handbook were highly matched and reliable in the same cohort. So, it also might be considered that the relation of their memories and exact presentation, delivery mode, and method could be matched and reliable. We have to take in mind that there are other factors that affect life-style-related diseases such as endogenous factors, hormones, cytokines or exogenous influences, infection, physical activities, social behavior, and other environmental factors[41]. Kwok *et al.* reports lower birth weight and greater infant weight gain typical of firstborns that could program metabolism detrimentally[42]. Further, birth weight, gestational week, maternal smoking during pregnancy, and passive smoking in childhood also affect future cardiovascular risks[43, 44]. Although we have proved that feeding type after birth affects the future cardiovascular risks, it is suggested that lactation is associated with maternal occupation, which we could not investigate[45]. The results of this current study may be different when we consider all of these as confounding factors. However, we could not include all of these because we do not have enough data about these.

Conclusion

Our study proposed that perinatal conditions around birth such as delivery place, the presentation of a fetus, and the breastfeeding method were related to the future development of glucose intolerance and hyperlipidemia in Japanese women. These results have a large influence in viewpoint of preventive medicine as we revealed the high-risk groups for future cardiovascular diseases, and we should encourage these people to have medical examination.

Acknowledgments

We are indebted to the nursing staff at the National Cerebral and Cardiovascular Center for their important contributions to the study.

Conflict of Interest

The authors declare no conflicts of interest in association with the study. Financial support was from institutional sources only.

Funding

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

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