

Review Article

Epidemiological Studies of the Developmental Origins of Adult Health and Disease in Japan: A Pediatric Perspective in Present Day Japan

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Abstract. The origins of adult disease are considered to relate to fetal undernutrition, and this concept is termed “developmental origins of adult health and disease” (DOHaD). Here, we describe several epidemiological studies performed in Japan and discuss whether DOHaD is applicable to children in present day Japan. In a study of healthy children and young adults, it was found that systolic blood pressure, total cholesterol and adiponectin were associated with birth weight. Hyperinsulinemia, high blood pressure, elevated transaminase levels and prevalence of metabolic syndrome in obese children were inversely correlated with birth weight and positively correlated with current weight and waist circumference. Birth weight was related to the development of type 2 diabetes in children. DOHaD is therefore considered to be applicable in Japan. The key considerations of DOHaD are the following two mismatches. The first mismatch pertains to growth and development in response to environmental influences, especially those of nutrition. The second mismatch pertains to the prenatal versus postnatal environment. We consider that the chance of children in present day Japan developing adult diseases is determined by the above mismatches. Pediatricians and schoolteachers should therefore understand the concept of DOHaD, so that they can educate both children and their families regarding an appropriate diet to reduce the likelihood of developing adult diseases in later life.

Key words: birth weight, obesity, blood pressure, insulin, adiponectin

Introduction

The prevalence of obesity in Japanese children and adolescents has increased from 5%

to more than 10% over the last two decades. This has become a serious public health concern, as childhood obesity, which is the leading cause of hyperinsulinemia and insulin resistance, is associated with adult diseases such as hypertension (HT), dyslipidemia, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS) in adulthood. These diseases are caused by both genetic factors and postnatal environmental factors. The latter factors, the so-called “lifestyle factors”, are more closely related to the development of adult diseases than genetic

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factors. This has been demonstrated by the recent rapid increase in fat consumption in Japan. Leading an adequately healthy lifestyle from childhood will reduce the likelihood of developing obesity and prevent certain adult diseases. Therefore, pediatricians should be concerned with the health education of children and adolescents in order to prevent the possibility of obesity in later life.

In 2004, Barker *et al.* proposed the concept of “developmental origins of adult health and disease” (DOHaD), which considers that intrauterine growth restriction (IUGR) is associated with an increased risk of developing MS and its related diseases in later life (1). The supply of nutrients to the fetus is the major determinant of fetal growth and is dependent on the mother’s size, body composition, nutrient store, diet during pregnancy, and the transport of nutrients to the placenta and their subsequent transfer across the placental membrane. DOHaD suggests that health education for children and adolescents is important to prevent them from bearing offspring who will be at risk of developing MS and its related diseases because maintaining a healthy lifestyle is necessary for mothers to prevent IUGR. In this paper, we briefly review several epidemiological studies of Japanese children, adolescents and adults and discuss the applicability of DOHaD in present day Japan (Table 1). As DOHaD was shown to be applicable in Japan, the need for appropriate health education for both children and adolescents is emphasized.

DOHaD in healthy Japanese children and young adults

Previously, we reported the relationship of birth weight and current body weight with blood pressure (BP) in 195 healthy 3-yr-old Japanese children from Niigata, Japan (2). Systolic blood pressure (SBP) was inversely correlated with weight at birth and positively correlated to weight at 3 yr of age. Children at 3 yr of age

whose birth weights were more than 3,520 g had a mean SBP of 3.0 mmHg below that of those whose birth weight was 2,999 g or less. Mean SBP at 3 yr of age for children whose weight at 3 yr exceeded 16.8 kg was 9.4 mmHg higher than that of age-matched children whose weight was 14.2 kg or less. We also found an increase of 0.12 mmHg in the SBP of children for each increment of 1 mmHg in the SBP of their mothers. The SBP at 3 yr of age in children of mothers who had experienced pretibial edema during pregnancy (101.0 ± 8.8 mmHg) was significantly higher than that in children whose mothers did not have edema (96.6 ± 9.6 mmHg).

Kaneshi *et al.* reported the relationship of birth weight or weight velocity (weight gain/year) with risk factors of atherosclerosis in 330 Japanese children (187 boys, 143 girls) between 7 and 12 yr of age who underwent screening for lifestyle-related diseases in Okinawa, Japan (3). Birth weight was significantly correlated with serum levels of adiponectin ($r=0.239$, $p=0.000$), uric acid ($r=-0.247$, $p=0.000$) and high-density lipoprotein cholesterol (HDL-C; $r=0.117$, $p=0.034$) after adjusting for age, sex and body mass index (BMI) percentile. However, weight velocity was a stronger predictive variable than birth weight for both adiponectin and uric acid.

Miura *et al.* reported the relationship of birth weight, current weight, rate of height increase from 3 yr to 20 yr of age and BP with serum total cholesterol (TC) level in 4,626 Japanese (2,198 men, 2,428 women) at 20 yr of age and born between 1965 and 1974 in Ishikawa, Japan (4). Using multiple linear regression analysis, the authors estimated that a higher birth weight (+1 standard deviation) was significantly associated with SBP (lower by 1.6 mmHg in men and by 1.0 mmHg in women) and serum TC (lower by 0.07 mmol/l in men and by 0.04 mmol/l in women) after adjusting for current weight and rate of height increase.

Suzuki *et al.* reported the relationship of birth weight and BP with serum lipid levels in 299 (207 men, 92 women) medical students of

Table 1 Epidemiological studies of the relation of birth weight and risks factors to cardiovascular disease in Japan

Author	Year	Study design	Region	Subjects	Independent variables	Dependent variables	Results (significant correlation)
Hashimoto N. <i>et al.</i> ²⁾	1996	Retrospective, cross-sectional	Niigata	Healthy children, 3 yr old, 99 boys and 96 girls	BW, BH, cBW, SBP of mother, edema of mother	SBP	BW: inverse SBP and edema: positive
Kaneshi T. <i>et al.</i> ³⁾	2007	Retrospective, cross-sectional	Okinawa	Healthy children, 7–12 yr old, 187 boys and 143 girls	BW, age, cBMI percentile, sex	HDL-C, UA, adiponectin, PG, insulin, TC, LDL-C, TG, LDLsize	HDL-C, UA: inverse adiponectin: positive
Miura K. <i>et al.</i> ⁴⁾	2001	Retrospective, cross-sectional	Ishikawa	Healthy young adults, 20 yr old, 2,198 men and 2,428 women	BW, cBW, height increase	SBP, DBP, TC	BW and BP: inverse BW and TC (men): inverse Height increase and BP, TC: inverse
Suzuki T. <i>et al.</i> ⁵⁾	2000	Retrospective, cross-sectional	Tochigi	Healthy young adults, 19–31 yr old, 207 men and 92 women	BW, cBMI, age, smoking	SBP, DBP, TC, TG	BW and SBP, DBP: inverse
Hiura M. <i>et al.</i> ⁸⁾	2001	Retrospective, cross-sectional	Niigata	Obese children, 6–15 yr old, 128 boys and 52 girls	BW, BW Z score	Insulin, HOMA-R	BW Z score and HOMA-R (boys): inverse BW, BW Z score (girls): inverse
Tanaka Y. <i>et al.</i> ⁹⁾	2005	Retrospective, cross-sectional	Niigata	Obese children, 6–15 yr old, 650 boys and 317 girls	BW, BW Z score, Pmax	Insulin, HOMA-R	BW, BW Z score: inverse
Abe Y. <i>et al.</i> ¹¹⁾	2007	Retrospective, cross-sectional	Niigata	Obese children, 9–12 yr old, 97 boys and 29 girls	BW, cBW, cBH, age	SBP, DBP, insulin, GPT, HDL-C, LDL-C, TG, FPG, HbA1c	BW and SBP, DBP, insulin, GPT: inverse
Kikuchi T. <i>et al.</i> ¹⁰⁾	2008	Retrospective, cross-sectional	Niigata	Obese children, 6–15 yr old, 600 boys and 283 girls	BW, BW Z score, WC, sex, age	Insulin, adiponectin, GPT, SBP, DBP, TG, HDL-C, LDL-C	BW, BW Z score and insulin, GPT: inverse BW, BW Z score and adiponectin: positive
Tamakoshi T. <i>et al.</i> ⁶⁾	2006	Retrospective, cross-sectional	Aichi	Healthy adult, 35–65 yr old, 2,349 men and 758 women	BW, cBMI, age, sex, family history of HT, smoking, drinking, exercise activity level	HT	BW: inverse
Tamakoshi T. <i>et al.</i> ⁷⁾	2006	Retrospective, cross-sectional	Aichi	Healthy adult, 35–65 yr old, 1,661 men and 616 women	BW, cBMI, age, sex, smoking, drinking, exercise level	Adiponectin	BW: positive
Sugihara S. <i>et al.</i> ¹⁵⁾	2008	Retrospective, cross-sectional	All Japan	T2DM, 9–17 yr old, 121 boys and 138 girls	BW	Distribution of BW	BW: U-shape, BW<2,500 g, BW>4,000 g: high prevalence of T2DM

BW: birth weight BH: birth height cBW: current body weight cBH: current body height cBMI: current body mass index WC: waist circumference SBP: systolic blood pressure DBP: diastolic blood pressure HT: hypertension TC: total cholesterol HDL-C: high density lipoprotein cholesterol LDL-C: low density lipoprotein cholesterol TG: triglyceride PG, plasma glucose GPT: glutamic pyruvic transaminase UA: uric acid HOMA-R: homeostasis model assessment-insulin resistance QUICKI: quantitative insulin sensitivity check index (QUICKI) T2DM: type 2 diabetes mellitus SBP of mother: systolic blood pressure during the last week of gestation edema of mother: edema during the last week of gestation.

Dokkyo University School of Medicine who had a mean age of 23 yr (5). In this case, male birth weight was inversely correlated with serum TC and triglyceride (TG) levels in young adulthood

and was independent of current BMI. However, the birth weight showed no relation with BP in this study.

These findings suggest the relation of birth

weight with BP, TC, HDL-C, uric acid and adiponectin. However, a study reported that birth weight was not associated with these risk factors of cardiovascular disease (5). To reveal the relationship of fetal and infant growth with these risk factors, further epidemiological study should be conducted in Japan.

DOHaD in middle-aged Japanese adults

Tamakoshi *et al.* reported the relationship of birth weight with adult HT in a Japanese workplace population (2,303 males, 804 females) aged 35 to 66 yr (6). Multiple logistic regression analysis adjusted for age, sex, BMI, parental history, and lifestyle revealed that the adjusted odds ratios for HT were 1.26 (95% confidence interval (CI): 0.88–1.80), 1.00 (reference), 0.89 (95%CI: 0.73–1.08) and 0.70 (95%CI: 0.49–1.00) for subjects who were in the birth weight categories of < 2,500 g, 2,500 ≤ 3,000 g, 3,000 ≤ 3,500 g, and > 3,500 g, respectively (p-value=0.009).

Tamakoshi *et al.* reported the relationship of birth weight with serum adiponectin levels in 2,277 subjects (1,661 men, 616 women) aged 35 to 66 yr (7). After adjusting for potential confounders, including age, sex, current BMI, smoking status, alcohol consumption and exercise activity level, the geometric mean adiponectin levels were 6.63, 6.45, 6.86, 7.05, 6.75 and 7.22 mg/ml for subjects with birth weights that were < 2,500, 2,500 to < 2,800, 2,800 to < 3,000, 3,000 to < 3,200, 3,200 to < 3,500 and > 3,500 g, respectively. Consequently, a positive association was found between birth weight and adiponectin concentration (p<0.002).

These findings suggest that the relations of weight and height at birth and postnatal weight increases with the risk factors of cardiovascular disease in middle-aged Japanese adults.

DOHaD in obese Japanese children and adolescents

We investigated the association of birth

weight with metabolic derangements in obese children in Niigata, Japan (8–11). We reported the relationships of birth weight and current visceral fat accumulation with hyperinsulinemia and insulin resistance in 967 obese Japanese children and adolescents (650 boys, 317 girls) aged 6 to 15 yr (9). We divided the subjects into 4 groups on the basis of their birth weight or standard deviation (SD) score and compared the following anthropometric measurements: maximum preperitoneal fat thickness of the abdominal wall (Pmax), BP, serum insulin levels, homeostasis model assessment-insulin resistance (HOMA-R) and quantitative insulin sensitivity check index (QUICKI) among the quartiles. The fasting serum insulin levels and HOMA-R were highest in the quartile with the lowest birth weight or SD score. Birth weight and SD score were inversely related to the serum insulin levels and HOMA-R but positively related to QUICKI after adjusting for Pmax. These findings suggest that both the intrauterine environment and current visceral fat accumulation are related to hyperinsulinemia, insulin resistance and the subsequent development of MS in obese Japanese children.

We also reported the relationship of birth weight with serum insulin, adiponectin, glutamic pyruvic transaminase (GPT), TG, HDL-C and low density lipoprotein cholesterol (LDL-C) levels (10). Multiple linear regression analyses adjusted for sex, age, and current waist circumference revealed a correlation of birth weight with serum adiponectin, insulin and GPT levels (Table 2). On the other hand, the serum TG, HDL-C, and LDL-C levels showed no relation to birth weight.

Moreover, we have reported on the relationships of current weight-to-birth weight ratio (WBWR) with BP, elevated GPT and hyperinsulinemia in 126 obese Japanese children and adolescents (97 boys, 29 girls; age range 9–12 yr) (11). The subjects were divided into an MS group and a non-MS group on the basis of criteria proposed for diagnosing Japanese children with

Table 2 Multiple regression analyses of adiponectin, insulin and GPT with birth weight and waist circumference adjusted for sex and age among 600 obese boys and 283 obese girls from Japan

Independent variables	Dependent variables	Adiponectin		Insulin		GPT	
		β	p	β	p	β	p
Model 1	Waist circumference	-0.235	<0.0001	0.591	<0.0001	0.453	<0.0001
	Birth weight	0.09	<0.01	-0.139	<0.0001	-0.131	<0.0001
Model 2	Waist circumference	-0.236	<0.0001	0.595	<0.0001	0.457	<0.0001
	Birth weight SD score	0.087	<0.01	-0.150	<0.0001	-0.14	<0.0001

GPT, glutamic pyruvic transaminase.

MS. Although there were no significant differences in age or anthropometric measurements between the two groups, the birth weight of the MS group was lower than that of the non-MS group, whereas the WBWR of the MS group was higher than that of the non-MS group. Systolic and diastolic blood pressure, serum insulin and GPT levels correlated positively with birth weight after adjusting for sex, current height and weight.

We then investigated the association of birth weight and current waist circumference with the prevalence of MS and serum insulin levels in obese children and adolescents. We divided 416 obese children (261 boys, 125 girls) into 9 groups on the basis of low, medium or heavy birth weight, or small, medium or large waist circumference. The group with the low birth weight and large waist circumference had the highest prevalence of MS and mean serum insulin level among the 9 groups (Tables 3 and 4).

These findings suggest that birth weight is related to metabolic derangements in obese Japanese children and adolescents. Ideally, epidemiological studies should be performed in other regions of Japan, because the presented studies have only performed in some regions.

DOHaD in Japanese children and adolescents with T2DM

According to epidemiological studies, interactions between birth weight and early postnatal growth have been associated with the development of diabetes in later life (12). Recent studies of Pima Indians and schoolchildren in Taiwan revealed a U-shaped relationship between birth weight and the risk of developing T2DM (13, 14). Sugihara *et al.* reported the associations of birth weight and clinical characteristics with childhood-onset T2DM (15, 16). The frequencies of low and high birth weights were higher among patients with T2DM than among those in a control group, producing a U-shaped distribution ($p < 0.05$). Low-birth-weight patients had a low prevalence of a family history of diabetes. In contrast, high-birth-weight patients had a higher prevalence of diabetic mothers who used medication that included insulin therapy ($p < 0.05$). These findings supported the notion that fetal growth is related to the development of T2DM in Japanese children and adolescents.

Key considerations and mechanisms of DOHaD

Fetal growth is constrained by the nutrients and oxygen provided by the mother. A poor intrauterine environment, such as that of a

Table 3 Prevalence of metabolic syndrome and the mean levels of fasting serum insulin in 261 Japanese obese boys according to birth weight and waist circumference after being divided into 3 groups

Waist circumference (cm)	Birth weight (g)			Total
	1,740–3,120	3,130–3,425	3,430–4,875	
64.0–82.0	4 (10.8%)	0 (0.0%)	1 (3.8%)	5 (5.6%)
	<i>12.7</i>	<i>11.4</i>	<i>11.4</i>	<i>11.9</i>
	37	27	26	90
82.5–88.5	7 (29.2%)	3 (10.3%)	6 (18.2%)	16 (18.6%)
	<i>17.4</i>	<i>13.4</i>	<i>12.8</i>	<i>14.3</i>
	24	29	33	86
89.0–116.0	9 (33.3%)	8 (26.7%)	5 (17.9%)	22 (25.9%)
	<i>30.8</i>	<i>22.5</i>	<i>20.2</i>	<i>24.4</i>
	27	30	28	85
Total	20 (22.7%)	11 (12.8%)	12 (13.8%)	43 (16.5%)
	<i>19.5</i>	<i>16.0</i>	<i>14.7</i>	<i>16.8</i>
	88	86	87	261

Upper stand: number with metabolic syndrome (%). *Middle stand: the mean level of fasting serum insulin ($\mu\text{U}/\text{ml}$).* Lower stand: total number in each group.

Table 4 Prevalence of metabolic syndrome and the mean levels of fasting serum insulin in 125 Japanese obese girls according to birth weight and waist circumference after being divided into 3 groups

Waist circumference (cm)	Birth weight (g)			Total
	1,845–3,040	3,044–3,375	3,390–4,000	
69.0–80.5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	<i>15.0</i>	<i>16.4</i>	<i>17.8</i>	<i>16.4</i>
	12	19	11	42
86.0–85.5	3 (20.0%)	1 (11.1%)	0 (0.0%)	4 (10.0%)
	<i>20.5</i>	<i>20.3</i>	<i>19.6</i>	<i>20.1</i>
	15	9	16	40
86.0–114.5	11 (73.3%)	1 (7.7%)	2 (13.3%)	14 (32.6%)
	<i>32.8</i>	<i>23.7</i>	<i>21.5</i>	<i>26.1</i>
	15	13	15	43
Total	14 (33.3%)	2 (4.9%)	2 (4.8%)	18 (14.4%)
	<i>23.3</i>	<i>19.6</i>	<i>19.8</i>	<i>20.9</i>
	42	41	42	125

Upper stand: number with metabolic syndrome (%). *Middle stand: the mean level of fasting serum insulin ($\mu\text{U}/\text{ml}$).* Lower stand: total number in each group.

mother with malnutrition, a smoking habit or an inappropriate diet, will result in fetal growth retardation. When the maternal-placental nutrient supply fails to match the fetal nutrient demand, the fetus adapts to the poor nutrition by changing its metabolism, altering its secretion of hormones and the sensitivity of tissues to these hormones, redistributing its blood flow to protect key organs, especially the brain, and slowing its growth rate. Although this adaptation called “programming” is beneficial for fetal survival, it permanently alters the structure and function of both the tissues and the body of the newborn.

The downstream effects of poor fetal nutrition include insulin resistance in muscle, liver and adipose tissue, poor development of pancreatic β -cell mass and function, decreased replication of kidney cells and reduced activity of placental 11β -hydroxysteroid dehydrogenase (11β -HSD) type 2 (17). This programming is considered to be the individual’s adaptation to the mismatch of nutrition during growth and development in the fetal stage. Moreover, the second mismatch of the prenatal versus the postnatal environment will contribute to an increase in risk factors for developing adult disease. The underlying mechanisms of this innate programming involve epigenetic modifications to the non-imprinted genes and are induced by aspects of the developmental environment, which modify gene expression without altering the DNA sequence (18).

A pediatric perspective for DOHaD in present day Japan

In Japan, as of 2005, the average birth weight has decreased to <3,000 g, while the incidence of low-birth-weight infants has increased to 9.5%. The maternal diet has become insufficient, as the average daily energy intake is around 1,700–1,880 kcal and is not increased during pregnancy. Such a poor nutritional condition, which is often associated with a

western lifestyle, is expected to result in a trend of increased risk for present day Japanese children developing adult diseases in later life. Pediatricians and schoolteachers should therefore understand the concept and importance of DOHaD and educate both children and their families regarding appropriate diet to reduce the likelihood of developing adult diseases in later life.

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