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Low birthweight is associated with type 2 diabetes mellitus in Japanese adults: The Toon Health Study

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ABSTRACT

Aims/Introduction: Low birthweight is reportedly associated with type 2 diabetes mellitus; however, this association has not been confirmed in the Japanese population, and whether high birthweight is associated with type 2 diabetes mellitus is controversial. We aimed to investigate the association between birthweight and type 2 diabetes mellitus among a general Japanese population.

Materials and Methods: Overall 1,135 middle- to old-aged Japanese men and women were enrolled in the Toon Health Study. A 75-g oral glucose tolerance test was used to diagnose type 2 diabetes mellitus, and a questionnaire survey about birthweight was administered. The association between birthweight and the prevalence of type 2 diabetes mellitus in later life of the participants was examined using multivariable logistic regression analysis. Stratified analysis by current body mass index was also carried out.

Results: The mean age was 56.5 ± 12.2 years. Type 2 diabetes mellitus was observed in 9.3% of the participants in this study. Compared with the reference group (2,500–3,999 g), the adjusted odds ratio of the low-birthweight group (<2,500 g) for type 2 diabetes mellitus was 2.46 (95% confidence interval 1.48–4.10). The association between the high-birthweight group (≥4000 g) and type 2 diabetes mellitus was not significant after including family history of diabetes in the multivariable model. The odds ratio of the low-birthweight group for type 2 diabetes mellitus was higher in the overweight/obese group than in the non-overweight group.

Conclusions: Low birthweight was associated with an increased risk of type 2 diabetes mellitus in a Japanese population, especially in overweight/obese individuals.

INTRODUCTION

The association between birthweight and the development of type 2 diabetes mellitus later in life has been extensively investigated, particularly in Western countries. The previous studies showed that low birthweight (LBW) was a significant risk factor for type 2 diabetes mellitus, but whether high birthweight (HBW) also contributes to the development of type 2 diabetes mellitus is controversial[1–3]. Several studies have addressed the association between birthweight and type 2 diabetes mellitus in Japan[4–7], none of which were carried out based on an accurate diagnosis of type 2 diabetes mellitus using a 75-g oral glucose tolerance test (75-g OGTT).

The developmental origins of health and disease hypothesis proposes that the environmental status during the fetal and infant stage affect the quality of health and onset of diseases throughout life[8]; undernutrition status *in utero* results in small for gestational age fetuses, which might be programmed live in similar adverse environments after birth. However, if the environment changes and they start living in an affluent society later in life, this might result in a mismatch, which could lead to a risk factor for non-communicable diseases, including type 2 diabetes mellitus, hypertension, obesity, dysfunction of lipid

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metabolism and cardiovascular diseases. Although this hypothesis is well recognized as the underlying mechanism associating birthweight with type 2 diabetes mellitus, little evidence exists regarding the actual effect of birthweight on biochemical markers, including carbohydrate and lipid metabolism.

In Japan, the prevalence of LBW infants, as well as the number of patients with type 2 diabetes mellitus, has been increasing since the 1980s[9,10], which might lead to the onset of noncommunicable diseases and the associated economic burdens in Japan in the near future. Therefore, there is an urgent need to identify the pathogenetic mechanisms of type 2 diabetes mellitus and to establish preventive strategies. Thus, the present study aimed to investigate the association between birthweight and the development of type 2 diabetes mellitus according to 75-g OGTT, and the effect of birthweight on carbohydrate and lipid metabolism in the Japanese general population.

METHODS

Study participants

The Toon Health Study commenced in 2009, as a prospective community-based cohort study designed to identify the risk factors related to type 2 diabetes mellitus and cardiovascular disease. Toon City is a suburban area of the Ehime Prefecture on Shikoku Island located in southwestern Japan. Study participants who were voluntarily recruited from residents in Toon City aged 30–79 years underwent a physical examination, a blood test and a questionnaire survey. A detailed description of the study was previously established[11]. We carried out the present cross-sectional study as part of the Toon Health Study. Of the 2,032 participants enrolled in the baseline survey between 2009 and 2012, 1,461 participants underwent the second survey from 2014 to 2018. Additionally, 381 new enrollees participated in the second survey between 2014 and 2018. A diabetes examination was carried out in each survey. We conducted a questionnaire survey on birthweight among participants of the second survey (n = 1,842). In 2016, we sent the birthweight questionnaire to the individuals who had participated in the second survey between 2014 and 2015. Participants between 2016 and 2018 answered the above questionnaires at the time of the physical examination.

Of the 1,842 participants in the second survey, those who relocated to other cities (n = 11), who did not return the birthweight questionnaire (n = 435) and those who did not remember their birthweight (n = 261) were excluded. Finally, 1,135 men and women were included in the present study (Figure 1). This study was approved by the Human Ethics Review Committees of Ehime University Graduate School of Medicine (approval no. 1705011), and carried out in accordance with the Declaration of Helsinki. We confirmed written informed consent from all the participants.

75-g OGTT and definition of diabetes

Study participants underwent a 75-g OGTT, except those who were pharmacologically treated for diabetes. Blood samples were collected at baseline after at least 10 h of fasting, 1 and 2-h after ingestion of oral glucose. Plasma glucose levels were measured using the hexokinase method (Sysmex, Kobe, Japan). Glycosylated hemoglobin A1c was measured using the latex immuno-agglutination method (Kyowa Medex Co., Ltd., Tokyo, Japan). Insulin was measured using the electrochemiluminescence method in ECLusys (Roche Diagnostics, Tokyo, Japan). Serum triglyceride (TG) levels were measured by enzymatic methods. Low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels were measured using the direct homogeneous method. In the present study, type 2 diabetes mellitus and prediabetes were diagnosed in accordance with the American Diabetes Association criteria[12]. Type 2 diabetes mellitus was defined as fasting plasma glucose level of ≥126 mg/dL, 2-h postprandial glucose level of ≥200 mg/dL or current use of antihyperglycemic agents, and fasting insulin level of ≥0.6 μU/mL. Prediabetes was defined as fasting plasma glucose level of 100–125 mg/dL or 2-h postprandial glucose level of 140–199 mg/dL.

The homeostasis model assessment index for insulin resistance (HOMA-IR) was calculated as fasting insulin (μU/mL) × fasting glucose (mg/dL) / 405. The homeostasis model assessment of β-cell function (HOMA-β) was calculated as 360 × fasting plasma insulin (μU/mL) / fasting plasma glucose (mg/dL)[13]. We also used the Matsuda Index [10,000 / (fasting serum glucose × fasting serum insulin × mean OGTT glucose concentration × mean OGTT insulin concentration)$^{1/2}$][14] as an index of insulin sensitivity.

Birthweight and other covariates

A self-administered questionnaire was used to assess the birthweight, history of diabetes, current use of antihyperglycemic agents, family history of diabetes (parents and/or siblings), current drinking status and smoking status. Participants answered the birthweight questions based on recall or maternal and child health handbooks. They filled out the exact birthweight (g) or selected one of six categories (<2,000, 2,000–2,499, 2,500–2,999, 3,000–3,499, 3,500–3,999 and ≥4,000 g). Numerical birthweight data were converted into categorical data, because a majority of the participants (n = 857, 75.5%) selected categories rather than presenting actual numerical values. Birthweight data were categorized into three groups as follows: LBW group <2,500 g, as per the World Health Organization definition; normal birthweight group 2,500–3,999 g; and HBW group, ≥4,000 g, as the commonly used definition globally. Body mass index (BMI) was calculated as weight divided by height squared. Overweight and obesity were defined as BMI ≥25 kg/m^2 and BMI ≥30 kg/m^2, respectively. Systolic blood pressure and diastolic blood pressure were measured twice in the sitting position using an automatic sphygmomanometer after at least 5 min of rest. The mean of the two measurements was used for analysis.

Statistical analysis

All biochemical measurements were skewed, though transformed using natural logarithms before the analyses. The

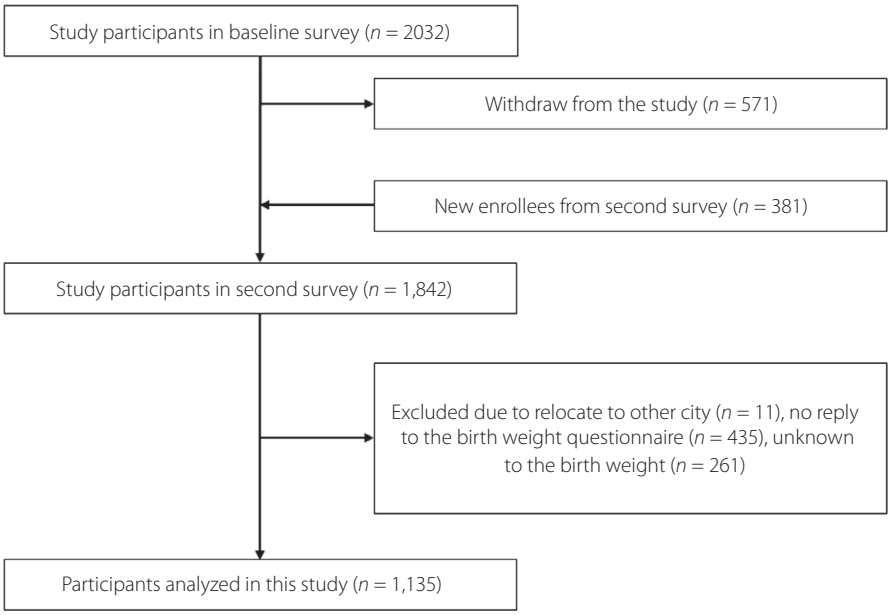

Figure 1 | Inclusion criteria and flow of enrollment of participants in the Toon Health Study.

characteristics of participants were summarized and compared between with and without type 2 diabetes mellitus. The Mann–Whitney *U*-test and χ^2-test were used for continuous variables and categorical variables, respectively. We also compared the differences of variables between the three birthweight groups using analysis of variance for mean values and χ^2-test for frequencies. Sex-, age- and BMI-adjusted means of biochemical measurements, HOMA-IR, HOMA-β and the Matsuda Index were calculated by analysis of covariance between the three birthweight groups, after excluding the participants taking medications for diabetes.

Multivariable logistic regression analyses were carried out to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for type 2 diabetes mellitus according to the category of birthweight, with birthweight of 2,500–3,999 g as the reference. The multivariable ORs were adjusted for age, sex, BMI, family history of diabetes, smoking status and drinking status. The analysis was repeated after excluding participants who were given antihyperglycemic agents.

We also carried out stratified analyses by BMI to investigate how current BMI contributes to the association between birthweight and development of type 2 diabetes mellitus. Participants were classified into one of six groups according to the combination of the three birthweight categories (<2,500, 2,500–3,999 and ≥4,000 g) and the two BMI categories (<25 and ≥25 kg/m^2). Multivariable logistic regression analysis was carried out with a combination of birthweight and BMI as the independent variable, with birthweight 2,500–3,999 g and BMI < 25 kg/m^2 as the reference group. The multivariable regression model was adjusted for age and sex.

Statistical significance was assumed at $P < 0.05$. All statistical analyses were carried out with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The mean age of the participants was 56.5 ± 12.2 years, and the mean BMI was 22.9 ± 3.4 kg/m^2; 33.6% of the participants were men. Table 1 summarizes the participant characteristics according to the presence and absence of type 2 diabetes mellitus. Type 2 diabetes mellitus was prevalent in 9.3% of the participants (12.3% in men and 7.8% in women). The average age, BMI, proportion of men and family history of diabetes were statistically significantly higher in the diabetes group (n = 106) than in the non-diabetes group (n = 1,029).

The clinical characteristics of participants among each birthweight categories are shown in Table 2. The prevalence of type 2 diabetes mellitus for the LBW group, the normal birthweight group and the HBW group were 17.6, 7.9 and 14.8%, respectively. There were no significant differences in BMI, prevalence of overweight/obese status and family history of diabetes between the three birthweight categories. Age-, sex- and BMI-adjusted means of biochemical examination findings according to the birthweight categories are presented in Table 3. In the LBW group, 2-h postprandial glucose, fasting TG and 2-h postprandial TG showed significant higher values than in the normal birthweight and the HBW groups. There were no significant differences in Matsuda Index, HOMA-IR and HOMA-β between the three birthweight categories.

Table 4 shows the results of the multivariate analysis for ORs and 95% CIs of type 2 diabetes mellitus according to

Table 1 | Characteristics of the participants in the overall, type 2 diabetes group and non-diabetes group

	Overall (n = 1,135)	Type 2 diabetes (n = 106)	Non-diabetes (n = 1,029)
Age (years)	56.5 ± 12.2	65.2 ± 9.1	55.6 ± 12.1**
Men, *n* (%)	381 (33.6)	47 (44.3)	334 (32.5)*
Body mass index (kg/m^2)	22.9 ± 3.4	24.1 ± 3.5	22.8 ± 3.3**
Family history of diabetes, *n* (%)	251 (22.1)	41 (38.7)	210 (20.4)**
Current drinker, *n* (%)	652 (57.4)	62 (58.5)	590 (57.3)
Smoking status			
Never, *n* (%)	792 (69.8)	68 (64.2)	724 (70.4)
Current, *n* (%)	88 (7.8)	11 (10.4)	77 (7.5)
Past, *n* (%)	255 (22.5)	27 (25.5)	228 (22.2)
HbA1c (%)	5.5 (5.2–5.7)	6.2 (5.7–6.8)	5.4 (5.2–5.6)**
HOMA-IR	1.10 (0.75–1.65)	1.87 (1.11–2.97)	1.07 (0.74–1.56)**
HOMA-β	62.3 (45.0–87.2)	49.7 (28.6–83.8)	63 (46.6–87.4)**
LDLC (mg/dL)	118 (99–139)	114 (97–133)	118 (99–139)
HDLC (mg/dL)	61 (52–72)	57 (47–67)	62 (53–72)**
TG (mg/dL)	89 (65–126)	111 (80–155)	88 (65–120)**
SBP (mmHg)	124.1 ± 20.1	136.7 ± 20.6	122.8 ± 19.6**
DBP (mmHg)	75.2 ± 11.9	79.8 ± 11.2	74.7 ± 11.8**
Low birthweight†, *n* (%)	148 (13.0)	26 (24.5)	122 (11.9)**
High birthweight‡, *n* (%)	27 (2.4)	4 (3.8)	23 (2.2)

Data are expressed as the mean ± standard deviation or median (interquartile range). *P < 0.05. **P < 0.001 versus type 2 diabetes group. †Low birthweight is defined as <2,500 g. ‡High birthweight is defined as ≥4,000 g. DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin A1c; HDLC, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; LDLC, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

birthweight categories. Compared with the reference group (2,500–3,999 g), the age-, sex- and BMI-adjusted ORs of type 2 diabetes mellitus was 2.46 (95% CI 1.48–4.10) for the LBW group and 3.53 (95% CI 1.07–11.66) for the HBW group. This association remained significant even after further adjustment for family history of diabetes in the LBW group, whereas the association between HBW and type 2 diabetes mellitus was attenuated, and lost significance after such adjustment.

The age- and sex-adjusted ORs of type 2 diabetes mellitus for the combined categories of birthweight and current BMI are shown in Figure 2. Compared with the reference group (birthweight 2,500–3,999 g and BMI <25 kg/m^2), the adjusted ORs for type 2 diabetes mellitus in those with birthweight <2,500 g and BMI <25 kg/m^2 was 2.11 (95% CI 1.13–3.95). The adjusted ORs reached 7.35 (95% CI 3.04–17.78) in those with birthweight <2,500 g and BMI ≥25 kg/m^2. Although, participants whose BMI was ≥25 kg/m^2 had a significantly higher risk of type 2 diabetes mellitus regardless of birthweight, the adjusted ORs for type 2 diabetes mellitus particularly increased among the LBW group (OR 7.35, 95% CI 3.04–17.78) and the HBW group (OR 11.52, 95% CI 2.53–52.44).

When sensitivity analysis was carried out after excluding participants taking antihyperglycemic agents, marked change was not found in the association between the LBW group and

Table 2 | Clinical characteristics of participants in each of the three birthweight groups

	Birth weight			*P*-value
	<2,500 g (n = 148)	2,500–3,999 g (n = 960)	≥4,000 g (n = 27)	
Age (years)	58.4 ± 11.4	56.4 ± 12.2	48.7 ± 12.3	0.0006
Men, *n* (%)	49 (33.1)	322 (33.5)	10 (37.0)	0.92
Body mass index (kg/m^2)	22.7 ± 2.8	22.9 ± 3.5	23.7 ± 3.8	0.35
Overweight†, *n* (%)	22 (14.9)	190 (19.8)	7 (25.9)	0.33
Obesity‡, *n* (%)	4 (2.7)	34 (3.5)	2 (7.4)	0.33
Family history of diabetes, *n* (%)	38 (25.7)	206 (21.5)	7 (25.9)	0.46
SBP (mmHg)	125.4 ± 21.0	124.2 ± 20.0	113.1 ± 15.7	0.012
DBP (mmHg)	76.3 ± 12.2	75.2 ± 11.8	70.6 ± 11.3	0.067

Data are expressed as the mean ± standard deviation. †Overweight was defined as body mass index ≥25 kg/m^2. ‡Obesity was defined as body mass index ≥30 kg/m^2. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3 | Comparison of biochemical examination findings in each of the three birthweight groups

	Birthweight			*P*-value
	<2,500 g (*n* = 141)	2,500–3,999 g (*n* = 936)	≥4,000 g (*n* = 24)	
HbA1c (%)	5.5 (0.5)	5.5 (0.4)	5.3 (0.4)	0.11
HOMA-IR	1.3 (0.9)	1.3 (0.9)	1.2 (0.8)	0.51
HOMA-β	70.8 (37.8)	71.8 (44.7)	70.4 (30.0)	0.71
Matsuda Index	8.2 (4.9)	8.3 (4.7)	8.6 (3.4)	0.68
Fasting plasma glucose (mg/dL)	93.2 (13.3)	92.3 (10.1)	90.4 (11.1)	0.86
1-h postprandial glucose (mg/dL)	155.3 (52.0)	147.4 (48.2)	131.3 (47.7)	0.37
2-h postprandial glucose (mg/dL)	134.8 (45.7)	124.9 (39.0)	111.3 (35.6)	0.035
Fasting insulin (μU/mL)	5.6 (3.4)	5.7 (3.7)	5.1 (2.7)	0.52
1-h postprandial insulin (μU/mL)	54.4 (39.3)	56.4 (44.8)	53.0 (26.2)	0.76
2-h postprandial insulin (μU/mL)	54.4 (43.0)	50.5 (36.4)	43.1 (30.3)	0.38
Fasting triglyceride (mg/dL)	111.3 (66.4)	103.1 (59.5)	69.2 (33.4)	0.0003
2-h postprandial triglyceride (mg/mL)	98.2 (66.1)	92.6 (58.9)	65.2 (37.2)	0.0029
LDLC (mg/dL)	118.3 (31.1)	120.3 (29.5)	104.8 (26.8)	0.075
HDLC (mg/dL)	60.5 (13.9)	63.1 (14.6)	65.8 (12.2)	0.011
TCHO (mg/dL)	204.1 (33.6)	206.8 (32.4)	188.1 (27.5)	0.064

Values are shown as the mean (standard deviation). Values were adjusted for age, sex and body mass index using analysis of covariance. DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin A1c; HDLC, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; LDLC, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TCHO, total cholesterol.

Table 4 | Multivariable odds ratios for type 2 diabetes mellitus for each birthweight group

	Birthweight		
	<2,500 g (*n* = 148)	2,500–3,999 g (*n* = 960)	≥4,000 g (*n* = 27)
Cases of type 2 diabetes mellitus, *n* (%)	26 (17.6)	76 (7.9)	4 (14.8)
ORs (95% CI) adjusted for			
Age and sex	2.38 (1.44–3.95)	1.00 (Ref)	3.97 (1.21–13.02)
Age, sex and BMI	2.46 (1.48–4.10)	1.00 (Ref)	3.53 (1.07–11.66)
Age, sex, BMI and family history of diabetes	2.41 (1.43–4.05)	1.00 (Ref)	3.12 (0.88–10.92)
Age, sex, BMI, family history of diabetes, smoking status, and drinking status	2.38 (1.41–4.00)	1.00 (Ref)	3.10 (0.87–11.12)

BMI, body mass index; CI, confidence interval; OR, odds ratio.

type 2 diabetes mellitus. We also did not observe any significant association between the HBW group and type 2 diabetes mellitus (OR 1.55,; 95% CI 0.20–12.35), after adjustment for age, sex and BMI.

DISCUSSION

The present study showed that LBW was independently associated with an increased risk of type 2 diabetes mellitus based on accurate diagnosis with a 75-g OGTT in the Japanese cohort. This association was more apparent in overweight/obese individuals. We also showed that LBW was implicated in the carbohydrate and lipid metabolic changes. The present findings were consistent with those of previous studies from different populations and ethnic groups[1,2,15–17].

A recent global meta-analysis based on 49 studies showed a J-shaped association between birthweight and type 2 diabetes mellitus[3], with the lowest risk for type 2 diabetes mellitus reported for birthweights of 3,500–4,000 g. Previously, several studies from Japan had reported an inverse relationship between birthweight and diabetes[4,6,7]. For instance, the Japanese Nurses' Health Study showed a linear inverse relationship between birthweight and adult-onset diabetes.[7] Notably, most of the participants in that study were women aged in their 30s and 40s; therefore, the prevalence of diabetes was only 0.8% of the participants. Meanwhile, a U-shaped relationship between birthweight and type 2 diabetes mellitus was observed in Japanese children who were born around 1990[5], with similar results reported in Taiwanese schoolchildren who were born around 1980 and are racially similar to the Japanese[18]. In the present study, no conclusions were drawn on the association between HBW and type 2 diabetes mellitus. However, we suspect that differences in the year at birth and changes in the nutritional

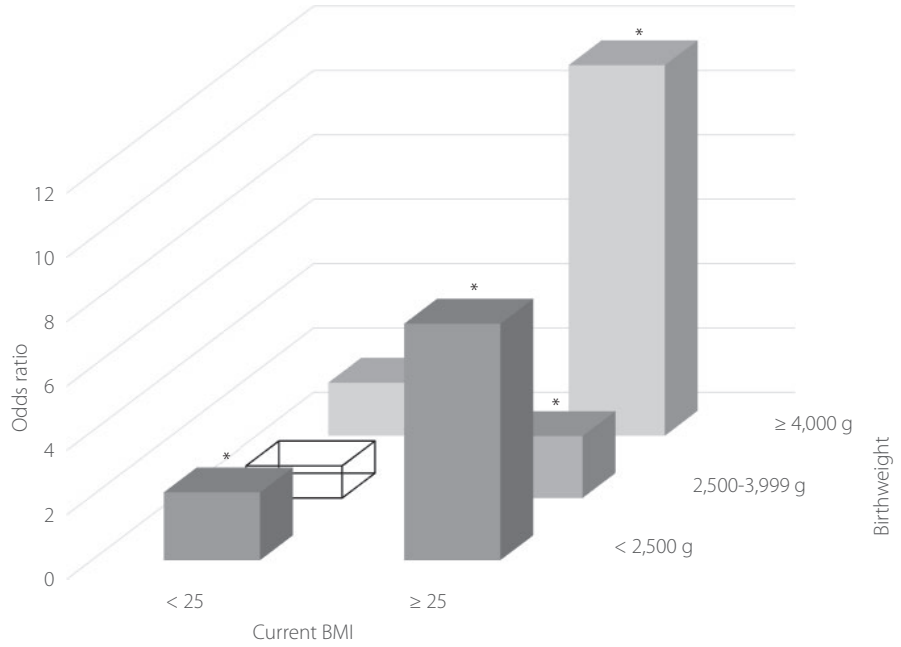

Figure 2 | Age- and sex-adjusted odds ratio of type 2 diabetes mellitus according to the combined categories of birthweight and current body mass index (BMI). *Statistically significant, $P < 0.05$. The reference was the combination group with a birthweight of 2,500–3,999 g and a BMI of <25 kg/m^2, shown as a transparent box.

intrauterine milieu might affect the role of HBW on the development of future diabetes. The median birth year of the participants was 1953 (range 1930–1987) in this study. Markedly increased consumption of fat in Japan after the 1960s has led to great changes in the maternal nutritional status, and hence the intrauterine environment. Further studies on the association between HBW and type 2 diabetes mellitus in young adults are required.

Obesity is a well-known major risk factor for type 2 diabetes mellitus. In the present study, the LBW group had a significantly higher risk of type 2 diabetes mellitus despite a normal current BMI. Furthermore, type 2 diabetes mellitus risk had increased dramatically in the LBW group if they were currently overweight or obese. Overweight or obesity might act as an effect modifier rather than a confounder on the association of LBW and subsequent type 2 diabetes mellitus. These findings fit the developmental origins of health and disease hypothesis, where LBW, which is a reflection of undernutrition *in utero*, encounters an environment of plentiful food or low energy expenditure, and there is increased risk of developing type 2 diabetes mellitus.

The pathophysiological mechanisms underlying the association between LBW and the development of type 2 diabetes mellitus later in life are not well understood. The present study showed higher serum levels of 2-h postprandial glucose, fasting TGs, and 2-h postprandial TGs in the LBW group than in the normal birthweight and the HBW groups. We also observed significant associations between LBW and type 2 diabetes mellitus or prediabetes when we carried out multivariable logistic regression analysis with type 2 diabetes mellitus and prediabetes as the outcome (data not shown). These findings suggest that LBW affects glucose and lipid metabolism, and induces the development of insulin resistance and type 2 diabetes mellitus. The present results provide supporting evidence to the findings of previous studies regarding the association between LBW and glucose intolerance[19–22].

Epigenetics, such as methylation of deoxyribonucleic acid (DNA), has been suspected as one possible mechanism underlying the developmental origins of health and disease hypothesis. Several studies have established the role of DNA methylation in the pathogenesis of type 2 diabetes mellitus[23,24]. There have also been reports on differences of DNA methylation in human tissues, such as the skeletal muscle and adipose tissue, which are involved in insulin resistance, between individuals with LBW and normal birthweight[25–28]. The reduced plasticity of regulation through epigenetics among people who were born with LBW might contribute to the development of insulin resistance and type 2 diabetes mellitus.

In Japan, the prevalence of LBW has been increasing since the 1980s[5]. Poor nutrition and gestational weight gain, and the desire to be slim in Japanese young women might contribute to lower birthweight[29]. In fact, the BMI in >20% of Japanese women aged in their 20s is <18.5 kg/m^2[29]. A previous study reported the intergenerational epigenetic inheritance in humans[30]. Epigenetic alterations in women born with LBW might be maintained and contribute to the manifestation of some phenotypes in their offspring. Nevertheless, other studies

have shown that healthy lifestyle habits, such as exercise and healthy diet, can alter DNA methylation status in human adipose tissue or skeletal muscle[31–36], suggesting that lifestyle changes can reverse these epigenetic modifications.

A major strength of the present study is that type 2 diabetes mellitus and prediabetes were diagnosed accurately using 75-g OGTT. Although several important confounders were controlled for, some residual or unmeasured confounding effects could not be completely ruled out.

This study had several limitations. First, there might be a selection bias. The study participants were volunteers in a single suburban city of Japan. The participants without birthweight information were older, had higher BMI and had a higher prevalence of type 2 diabetes mellitus than those who provided information on their birthweight. There is a possibility that the present study participants probably had higher health awareness than the general Japanese population. In contrast, the prevalence of type 2 diabetes mellitus in our survey was 12.3% in men and 7.8% in women, which was similar to the findings from the National Health and Nutrition Survey of Japan (individuals strongly suspected of having diabetes, 15.2% for men and 8.2% for women, in 2012)[37], and a previous epidemiological study in a rural area of Japan reported that diabetes was prevalent in 11.5% of the individuals aged 35–89 years between 2000 and 2002[38].

Second, a cross-sectional design of the present study did not allow us to show causality between LBW and type 2 diabetes mellitus. Third, the information on gestational age was not available; therefore, we could not distinguish between premature infants and growth-restricted infants. From the perspective of intrauterine undernutrition, the effect of fetal growth restriction might be more important on the development of type 2 diabetes mellitus later in life. Although several studies have suggested an association between fetal growth restriction and adult-onset diabetes[7,39], a Danish cohort study reported that both LBW and prematurity were independently associated with an increased risk of type 2 diabetes mellitus through different mechanisms[21].

Fourth, the validity of self-reported birthweight needs to be considered. A previous study showed a high correlation between self-reported birthweight and the actual birthweight, determining that the reported birthweight is reliable enough to be used in epidemiological studies[40]. A future prospective longitudinal study is required to investigate the association between fetal growth restriction or HBW and the development of type 2 diabetes mellitus.

In conclusion, LBW was associated with type 2 diabetes mellitus in the middle- to old- aged Japanese population. LBW contributed to the development of type 2 diabetes mellitus by affecting glucose and lipid metabolism. These results emphasize the importance of improving the nutritional status of pregnant women and implementing preventive strategies for people born with LBW. Further studies should lead to pre-emptive medicine to reduce the prevalence of non-communicable diseases.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Harder T, Rodekamp E, Schellong K, *et al*. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. *Am J Epidemiol* 2007; 165: 849–857.
2. Whincup PH, Kaye SJ, Owen CG, *et al*. Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* 2008; 300: 2886–2897.
3. Knop MR, Geng TT, Gorny AW, *et al*. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7 646 267 participants from 135 studies. *J Am Heart Assoc* 2018; 7: e008870.
4. Anazawa S, Atsumi Y, Matsuoka K. Low birth weight and development of type 2 diabetes in a Japanese population. *Diabetes Care* 2003; 26: 2210–2211.
5. Sugihara S, Sasaki N, Amemiya S, *et al*. Analysis of weight at birth and at diagnosis of childhood-onset type 2 diabetes mellitus in Japan. *Pediatr Diabetes* 2008; 9: 285–290.
6. Oya J, Nakagami T, Kurita M, *et al*. Association of birthweight with diabetes and insulin sensitivity or secretion in the Japanese general population. *J Diabetes Investig* 2015; 6: 430–435.
7. Katanoda K, Noda M, Goto A, *et al*. Impact of birth weight on adult-onset diabetes mellitus in relation to current body mass index: the Japan Nurses' Health Study. *J Epidemiol* 2017; 27: 428–434.
8. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science* 2004; 305: 1733–1736.
9. Ministry of Health, Labour and Welfare (Japan). Vital statistics of Japan. Tokyo: Health, Labor and Welfare Statistics Association , 2017 (Japanese).
10. The National Health and Nutrition Survey of Japan. Tokyo: Health, Labor and Welfare Statistics Association, 2017 (Japanese).
11. Tabara Y, Saito I, Nishida W, *et al*. Relatively lower central aortic pressure in patients with impaired insulin sensitivity and resistance: the Toon Health Study. *J Hypertens* 2011; 29: 1948–1954.
12. American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2019. *Diabetes Care* 2019; 42: S13–S28.
13. Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.
14. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999; 22: 1462–1470.

15. Hales CN, Barker DJ, Clark PM, *et al*. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991; 303: 1019–1022.
16. Barker DJ, Hales CN, Fall CH, *et al*. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993; 36: 62–67.
17. Carlsson S, Persson PG, Alvarsson M, *et al*. Low birth weight, family history of diabetes, and glucose intolerance in Swedish middle-aged men. *Diabetes Care* 1999; 22: 1043–1047.
18. Wei JN, Sung FC, Li CY, *et al*. Low birth weight and high birth weight infants are both at an increased risk to have type 2 diabetes among schoolchildren in Taiwan. *Diabetes Care* 2003; 26: 343–348.
19. Phillips DI, Barker DJ, Hales CN, *et al*. Thinness at birth and insulin resistance in adult life. *Diabetologia* 1994; 37: 150–154.
20. Lithell HO, McKeigue PM, Berglund L, *et al*. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ* 1996; 312: 406–410.
21. Pilgaard K, Færch K, Carstensen B, *et al*. Low birthweight and premature birth are both associated with type 2 diabetes in a random sample of middle-aged Danes. *Diabetologia* 2010; 53: 2526–2530.
22. Rønn PF, Jørgensen ME, Smith LS, *et al*. Associations between birth weight and glucose intolerance in adulthood among Greenlandic Inuit. *Diabetes Res Clin Pract* 2019; 150: 129–137.
23. Davegårdh C, García-Calzón S, Bacos K, *et al*. DNA methylation in the pathogenesis of type 2 diabetes in humans. *Mol Metab* 2018; 14: 12–25.
24. Muka T, Nano J, Voortman T, *et al*. The role of global and regional DNA methylation and histone modifications in glycemic traits and type 2 diabetes: a systematic review. *Nutr Metab Cardiovasc Dis* 2016; 26: 553–566.
25. Brøns C, Jacobsen S, Nilsson E, *et al*. Deoxyribonucleic acid methylation and gene expression of PPARGC1A in human muscle is influenced by high-fat overfeeding in a birth-weight-dependent manner. *J Clin Endocrinol Metab* 2010; 95: 3048–3056.
26. Gillberg L, Jacobsen SC, Rönn T, *et al*. PPARGC1A DNA methylation in subcutaneous adipose tissue in low birth weight subjects - Impact of 5 days of high-fat overfeeding. *Metabolism* 2014; 63: 263–271.
27. Jacobsen SC, Gillberg L, Bork-Jensen J, *et al*. Young men with low birthweight exhibit decreased plasticity of genome-wide muscle DNA methylation by high-fat overfeeding. *Diabetologia* 2014; 57: 1154–1158.
28. Gillberg L, Perfilyev A, Brøns C, *et al*. Adipose tissue transcriptomics and epigenomics in low birthweight men and controls: role of high-fat overfeeding. *Diabetologia* 2016; 59: 799–812.
29. Yoshida H, Kato N, Yokoyama T. Current trends in low birth weight infants in Japan. *J Natl Inst Public Health* 2014; 63: 2–16. (Japanese).
30. Pembrey M, Saffery R, Bygren LO. Human transgenerational responses to early-life experience: potential impact on development, health and biomedical research. *J Med Genet* 2014; 51: 563–572.
31. Hjort L, Jørgensen SW, Gillberg L, *et al*. 36 h fasting of young men influences adipose tissue DNA methylation of LEP and ADIPOQ in a birth weight-dependent manner. *Clin Epigenetics* 2017; 9: 40.
32. Barrès R, Yan J, Egan B, *et al*. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab* 2012; 15: 405–411.
33. Nitert MD, Dayeh T, Volkov P, *et al*. Impact of an exercise intervention on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes. *Diabetes* 2012; 61: 3322–3332.
34. Rönn T, Volkov P, Davegårdh C, *et al*. A six months exercise intervention influences the genome-wide DNA methylation pattern in human adipose tissue. *PLoS Genet* 2013; 9: e1003572.
35. Perfilyev A, Dahlman I, Gillberg L, *et al*. Impact of polyunsaturated and saturated fat overfeeding on the DNA-methylation pattern in human adipose tissue: a randomized controlled trial. *Am J Clin Nutr* 2017; 105: 991–1000.
36. Fabre O, Ingerslev LR, Garde C, *et al*. Exercise training alters the genomic response to acute exercise in human adipose tissue. *Epigenomics* 2018; 10: 1033–1050.
37. Ministry of Health, Labour and Welfare. Outline of the National Health and Nutrition Survey Japan, 2012 (Japanese).
38. Nakagami T, Tominaga M, Nishimura R, *et al*. Is the measurement of glycated hemoglobin A1c alone an efficient screening test for undiagnosed diabetes? Japan National Diabetes Survey. *Diabetes Res Clin Pract* 2007; 76: 251–256.
39. Hypponen E, Power C, Smith GD. Prenatal growth, BMI, and risk of type 2 diabetes by early midlife. *Diabetes Care* 2003; 26: 2512–2517.
40. Troy LM, Michels KB, Hunter DJ, *et al*. Self-reported birthweight and history of having been breasted among younger women: an assessment of validity. *Int J Epidemiol* 1996; 25: 122–127.