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ORIGINAL ARTICLE

Association of birthweight with diabetes and insulin sensitivity or secretion in the Japanese general population

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ABSTRACT

Aims/Introduction: Low birthweight (birthweight <2,500 g) has been considered to be a risk factor for diabetes in data from Western countries, and its percentage is increasing in Japan. The aim of the present study was to assess the association between birth weight and diabetes, as well as both insulin resistance and secretion.

Materials and Methods: The participants were 847 adults who underwent health check-ups. The participants were divided by birthweight into four groups (low birthweight and tertiles 1–3 above it). We assessed the effect of birthweight on diabetes using a logistic regression model. Multivariable liner regression analyses were carried out to examine whether birthweight is independently associated with homeostasis model assessment of insulin resistance and β-cell function.

Results: The prevalence of diabetes tended to increase with decreasing birthweight. The adjusted odds ratio for diabetes with low birthweight was 3.52 (1.04–11.96) as compared with the reference category, tertile 2. Univariable linear regression analyses showed that homeostasis model assessment of insulin resistance was negatively associated with birthweight, and this association remained after adjusting for age, sex, current body mass index and family history of diabetes. There was no significant association between homeostasis model assessment of β-cell function and birthweight.

Conclusions: Low birthweight was inversely associated with diabetes and insulin resistance in the Japanese general population. Longitudinal data analyses are required to examine the causal relationship between bodyweight and diabetes or insulin resistance in adulthood.

INTRODUCTION

In Japan, the percentage of babies with low birthweight (LBW), defined as birthweight (BW) <2,500 g, is increasing and the average BW is decreasing[1,2]. The proportion of LBW infants was 4.2% in 1980, 6.1% in 1990, 8.3% in 2000 and 9.6% in 2010[1,3]. This has been associated with an increase in smoking prevalence, a decrease in body mass index (BMI) in young women and aggressive management of weight gain in pregnancy[2,4]. Recently, LBW has been considered an independent risk factor for diabetes in studies from Europe and the USA[5–10], but data from Asia are limited[11–13]. The nature of the association between BW and diabetes was controversial because of ethnic differences and methodological differences in the statistical approach[5–10]. An unfavorable intrauterine environment might lead to future insulin resistance (IR) and β-cell dysfunction[14]. Japanese individuals are characterized by lower BMIs, but higher percentages of body fat than Caucasian individuals[15] and have lower insulin-secretory capacities[16]. Consequently, the effects of BW on insulin sensitivity and secretion in Japanese individuals might be different from those reported by previous studies in Europe and the USA. If the increased number of

LBW infants is a reason for the increasing number of diabetes patients in Japan, it is important for women to control body-weight and to modify their lifestyle during pregnancy. Thus, the aim of the present study was to assess the association between BW and diabetes and insulin sensitivity or secretion in people with LBW in a Japanese population.

MATERIALS AND METHODS

Participants

The study participants were 2,421 men and women who underwent general health examinations at Saitama-ken Saiseikai Kurihashi Hospital between October 2006 and September 2007. For the current analysis, individuals with missing information for BW ($n = 1,563$), those with missing data for fasting plasma glucose (FPG) or fasting insulin concentrations ($n = 8$) and those with missing data for relevant covariates ($n = 3$) were excluded. Thus, 534 men and 313 women were included in the analysis.

Measurements

In the present study, the health examination included self-administered questionnaires regarding family history of diabetes, physical examination and biochemical tests. All biochemical measurements were carried out at the same commercial laboratory (SRL, Hachioji, Tokyo, Japan). Blood samples were collected in the morning after a 10-h fast. FPG was measured using the hexokinase UV method with a 9000 automatic analyzer (JCA-BM2250; Hitachi, Tokyo, Japan). Fasting plasma immunoreactive insulin (F-IRI) was measured using an immunoradiometric assay (CLEIA, Lumipulse Presto II; Fuji Rebio, Tokyo, Japan). Height was measured to the nearest 0.1 cm with the participants standing without shoes. Bodyweight was measured to the nearest 0.1 kg with the participants dressed in light indoor clothing. BMI was calculated as the weight divided by the square of the height (kg/m^2). The BW information was collected by a questionnaire with inputs based on records in the maternal and child health notebook or the memory through the mother. The participants were divided into four groups by BW (LBW and tertiles [T] 1–3 above LBW): LBW, <2,500 g; T1, 2,500–3,000 g; T2, 3,001–3,200 g; and T3, >3,200 g. LBW was defined, according to the World Health Organization criteria, as <2,500 g.

The diagnosis of diabetes was based on self-reports by participants or a FPG level of ≥126 mg/dL (according to the World Health Organization 2006 FPG criteria)[17]. IR and insulin secretion were calculated on the basis of the FPG and F-IRI according to the homeostasis model assessment (HOMA)[18]: HOMA of IR (HOMA-IR) = FPG (mg/dL) × F-IRI (μU/mL) / 405 and HOMA of β-cell function (HOMA-B) = 360 × F-IRI / (FPG − 63).

Statistical Analysis

A χ^2-test was used to compare proportions, and Student's t-test or Mann–Whitney U-test was used to compare a continuous variable between men and women, and means of BW between participants with and without diabetes. The Armitage trend test was used to examine the trend in diabetes prevalence across the aforementioned four BW groups.

Multivariable logistic regression analyses were carried out to calculate P-values, odds ratios (ORs) and their 95% confidence intervals (95% CIs) for the effects of BW on diabetes, after adjusting for age (continuous), sex (categorical), current BMI (continuous) and family history of diabetes (categorical). When the four groups of BW were used as variables, each group was compared with T2.

Spearman's correlation coefficient analysis was used to evaluate the correlations between BW and anthropometric parameters or glucose metabolism. Participants taking medication for diabetes ($n = 20$) were excluded when analyzing data for plasma glucose, insulin concentrations, HOMA-IR and HOMA-B.

Univariable linear regression analyses were carried out to examine the association between HOMA-IR or HOMA-B and BW. Next, multivariable linear regression analyses were carried out to examine whether BW is independently associated with HOMA-IR. We chose HOMA-IR rather than HOMA-B, as HOMA-B was not significantly associated with BW in the univariable model. In the multivariable model, age, sex, current BMI and family history of diabetes were included as covariates as in the logistic model. Because of skewed distributions of HOMA-IR and HOMA-B, log-transformed values were used, which followed normal distributions more closely.

The study was approved by the institutional review board of Saitama-ken Saiseikai Kurihashi Hospital and Tokyo Women's Medical University, and informed consent was obtained from the participants.

Data were analyzed using SAS version 9.2 for Windows (SAS Institute, Cary, NC, USA). The P-values were based on two-sided tests, and the cut-off point for statistical significance was $P < 0.05$.

RESULTS

Characteristics of Study Participants

The average age and BMI were 47 ± 7 years and 23.5 ± 3.3 kg/m^2, respectively. The average BW was 3070 ± 430 g, and the prevalence of LBW was 5.3%. The participants with diabetes were older and had lower means of BW and HOMA-B, and higher means for current BMI, FPG and HOMA-IR than those without diabetes (Table 1).

Prevalence and Association of Diabetes and BW

The prevalence of diabetes tended to increase with decreasing BW (Table 2). The univariable logistic regression analysis showed that ORs (95% CIs) for the associations of diabetes with LBW, T1 and T3 were 3.76 (1.03–13.69, $P = 0.044$), 3.62 (1.50–8.73, $P = 0.004$) and 1.00 (0.34–2.91, $P = 0.999$), respectively, in comparison with those with T2 (Table 2). The corresponding values in the multivariable model were 3.52

Table 1 | Characteristics of study participants

	Total	Non-diabetes	Diabetes
n	847	807	40
Age (years)	47 ± 7	47 ± 7	49 ± 6***
Men, *n* (%)	534 (63.0)	500 (62.0)	34 (85.0)**
Current BMI (kg/m^2)	23.5 ± 3.3	23.4 ± 3.3	25.7 ± 3.8**
Birthweight (g)	3070 ± 430	3080 ± 429	2841 ± 390*
Fasting plasma glucose (mg/dL)	90 (85–97)	90 (85–96)	147 (125–172)*
Fasting insulin concentration (μU/mL)	5.36 (3.61–7.64)	5.22 (3.56–7.56)	7.56 (5.33–10.33)
HOMA-IR	1.20 (0.81–1.76)	1.18 (0.80–1.75)	2.61 (1.45–3.29)**
HOMA-B	72.3 (51.4–102.8)	72.7 (52.3–103.7)	44.7 (26.15–59.49)**
Family history of diabetes, *n* (%)	94 (11.1)	84 (10.4)	10 (25.0)***
Low birthweight, *n* (%)	44 (5.2)	40 (5.0)	4 (10.0)

For each continuous variable, mean ± standard deviation or median (interquartile) is shown. For each dichotomous variable, number (percent) is shown. Low birthweight is defined as <2,500 g. *$P < 0.001$, **$P < 0.01$, ***$P < 0.05$ vs non-diabetes. BMI, body mass index; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 2 | Prevalence and multiple odds ratios of diabetes according to four groups of birthweight

	Birthweight				*P for trend
	LBW <2,500 g	T1 2,500–3,000 g	T2 3,001–3,200 g	T3 >3,200 g	
n	44	247	326	230	
Cases of diabetes (%)	4 (9.1)	20 (8.1)	9 (2.8)	7 (3.0)	0.0002
Crude ORs (95% CIs)	3.76 (1.03–13.69)	3.62 (1.50–8.73)	1.00 (ref)	1.00 (0.34–2.91)	
Multivariable ORs (95% CIs)	3.52 (1.04–11.96)	3.10 (1.39–6.94)	1.00 (ref)	1.11 (0.41–3.01)	

Multiple models were adjusted for age, sex, current body mass index and family history of diabetes. Low birth weight (LBW) is defined as <2,500 g. Tertiles 1–3 are categories of normal birth weight: tertile 1 (T1) is 2,500–3,000 g, T2 is 3,001–3,200 g and T3 is >3,200 g. *Armitage trend test. CI, confidence intervals; ORs, odds ratios; T, tertile.

(1.04–11.96, $P = 0.044$), 3.10 (1.39–6.94, $P = 0.006$) and 1.11 (0.41–3.01, $P = 0.844$). The adjusted OR and its 95% CI for diabetes associated with a 1-kg/m^2 increase of current BMI was 1.14 (1.02–1.27, $P = 0.023$).

BW, Insulin Sensitivity and Insulin Secretion

BW was significantly and negatively correlated with age, F-IRI and HOMA-IR, and positively correlated with current BMI (Table 3).

Univariable linear regression analyses showed that HOMA-IR was negatively associated with BW, whereas HOMA-B was not. This significant association between BW and HOMA-R remained after adjusting for age, sex, current BMI and family history of diabetes. HOMA-IR was positively and independently associated with current BMI (Table 4).

DISCUSSION

The present study has shown that BW was inversely and independently associated with diabetes and HOMA-R, whereas HOMA-B was not significantly associated with BW in the

Table 3 | Spearman's correlation coefficients between birthweight and anthropometric parameters or glucose metabolism

	ρ	*P*-value
Age (years)	–0.076	0.027
Current BMI (kg/m^2)	0.082	0.016
Fasting plasma glucose (mg/dL)	–0.002	0.992
Fasting insulin concentration (μU/mL)	–0.111	0.038
HOMA-IR	–0.105	0.041
HOMA-B	–0.033	0.405

Participants taking medication for diabetes (*n* = 20) were excluded when analyzing data for glucose metabolism. BMI, body mass index; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

Japanese general population. Many previous studies reported inverse, linear associations between BW and diabetes[6,19]. However, some investigators claimed that low and high BW are associated with diabetes, and that BW shows a U-shaped relationship with diabetes prevalence[5,20]. One possible explanation

Table 4 | Factors affecting homeostasis model assessment of insulin resistance analyzed using a multivariable regression model

	Partial regression coefficient (B)	Standard error	Standardized partial regression coefficient (β)	*P*-values
Birthweight (1 kg)	−0.155	0.023	−0.123	<0.001
Age (1-year-old)	0.030	0.002	0.023	0.488
Sex (men vs women)	−0.076	0.043	−0.061	0.082
Current BMI (1 kg/m^2)	0.601	0.006	0.605	<0.001
Family history of diabetes (no vs yes)	0.057	0.061	0.044	0.191

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance.

for this discrepancy is that native North Americans have a high prevalence of diabetes and obesity from a young age, which leads to a high prevalence of gestational diabetes[20]. Although ethnic and genetic factors[21] might affect the association between BW and diabetes, these reports were consistent with the notion that LBW is positively associated with the risk of type 2 diabetes. The present results also suggested the association between LBW and diabetes is independent of current BMI. To our knowledge, this is the first study to assess the relationship between BW and diabetes in the Japanese general population. Regarding another study from Japan, Anazawa *et al.*[11] investigated hospital-based data and occupational cohort data of middle-aged men, and showed that the prevalence of LBW was higher among patients with diabetes than those without diabetes. The findings in the present study were consistent with those of the aforementioned study in that LBW as well as current high BMI were important risk factors for diabetes.

Glucose intolerance is characterized by both increased IR and decreased insulin secretion[22]. Most previous studies that reported an inverse association between BW and measures of IR used the intravenous glucose tolerance test and minimal model analysis[23,24]. When IR was measured using the euglycemic-hyperinsulinemic clamp technique, insulin sensitivity was decreased by approximately 20% in LBW participants compared with normal BW individuals[25]. Studies from Asia[26,27] also showed that the insulin sensitivity index was positively correlated with BW. In the present study, multiple regression analysis showed the association between HOMA-IR and BW was independent of current BMI. Data on the relationship between BW and insulin secretion are inconsistent[14,22,23,27–29]. It was hypothesized that fetal malnutrition was mediated through programming of the development of the pancreas, leading to impaired β-cell function[26]. Many previous reports, including several from Asia[22,23,27,29], showed no defect in β-cell function, but some[14,28] reported reduced insulin secretion in LBW participants. In the present study, HOMA-B had no significant association with BW. Because the insulin-secretory capacity in Asians is estimated to be relatively lower than that in Western populations[16], the compensatory ability of β-cells against IR might be limited in cases of high BMI.

Several mechanisms have been proposed to explain the association of LBW with diabetes and IR. According to the thrifty-phenotype hypothesis[30], inadequate *in utero* nutrition and environment favors developmental adaptations, generating a thrifty metabolism and leading to the development of resistance to insulin-stimulated glucose uptake in later life. However, the underlying mechanism of this hypothesis is unclear. A poor intrauterine environment might cause epigenetic alterations, such as deoxyribonucleic acid methylation[31]. On the basis of biopsy analysis in LBW and normal BW individuals, Schultz *et al.*[32] reported that LBW individuals showed significantly reduced leptin gene expression and an increased level of deoxyribonucleic acid methylation of the *LEP* promoter during preadipocyte differentiation. They also found a lower messenger ribonucleic acid expression of peroxisome proliferator-activated receptor-γ2 and glucose transporter type 4 in LBW individuals. Leptin is an important adipokine, and could link early nutrition to IR and diabetes[33]. Because the process of adipocyte differentiation begins *in utero* and continues to adulthood, these results suggest that LBW individuals might have dysregulated adipocyte function that leads to IR and diabetes. Furthermore, intrauterine growth restriction might change the set point and cause overactivation of the hypothalamic–pituitary–adrenal axis[34].

The present study had several limitations. First, there might be a selection bias. When comparing characteristics in participants with and without information of BW, participants with information of BW were younger, had lower FPG, and a lower proportion of men and diabetes compared with those without information of BW (data not shown). This would make our participants healthier than the general population, and thus our results are conservative. Second, we used self-reported questionnaires to obtain the data on BW. We understand that the inclusion of the reported BW might cause a bias if the deviation of the reported BW from the real BW is associated with, for example, glucose intolerance. Ideally, all BW data should be obtained from records; however, the power would have been fatally damaged because of a small sample size when we had included only the recorded data. Just as the present study, previous studies[6,7,11] have also included the reported BW, and shown the association between self-reported BW and glucose intolerance. Furthermore, one study showed that the Spearman's correlation between self-reported and recorded BW was 0.74[35]. Although our data of BW were obtained from both records in the maternal and child health notebook and their

memories through the mothers, our total BW data were approximately normally distributed. In the alternative analysis applying cut-off points based on quartiles of BW (<2,800, 2,801–3,010, 3,011–3,350, >3,351 g), the adjusted ORs (95% CIs) for diabetes in participants with 1st, 2nd and 4th quartiles of BW were 3.55 (1.40–8.98), 1.78 (0.63–4.98), and 0.48 (0.19–1.69), respectively, compared with the 3rd quartile, thereby suggesting that a lower BW is a significant and independent risk factor of diabetes. Prospective and longitudinal studies are required to confirm our results using accurate information for BW. Third, it was cross-sectional study; thus, longitudinal data need to be analyzed in the future. Fourth, the oral or intravenous glucose tolerance test and the hyperinsulinemic-euglycemic clamp technique are the standard techniques to measure IR and insulin secretion. Thus, HOMA-B provides a surrogate measure of insulin secretion, and therefore, the present results need to be confirmed in further studies. Because our data were obtained from participants in general health check-ups, it was not possible to carry out such expensive, invasive and long-sustained examinations. HOMA can be reliably used in large-scale or epidemiological studies in which only a fasting blood sample is available to assess IR; HOMA reflects 65% of the variability in IR as assessed by the glucose clamp technique[36].

In conclusion, the present cross-sectional study has shown that BW was inversely and independently associated with diabetes and IR in the Japanese general population. Longitudinal data analyses are required to examine the causal relationship between BW and diabetes or IR in adulthood.

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