# Low Birth Weight and High Birth Weight Infants Are Both at an Increased Risk to Have Type 2 Diabetes Among Schoolchildren in Taiwan

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**OBJECTIVE** — To study the effect of birth weight on risk of type 2 diabetes in the schoolchildren in Taiwan.

**RESEARCH DESIGN AND METHODS** — From 1992 to 1997, all schoolchildren aged 6–18 years were screened for diabetes in Taiwan Province. This cohort consisted of 1,966 patients with diabetes and 1,780 randomly selected subjects with normal fasting glycemia (NFG). Questionnaire interviewing was designed to classify diabetes. The birth weight was obtained from the Taiwan's Birth Registry. After merging the data, there were 978 subjects, including 429 with type 2 diabetes and 549 with of NFG enrolled in the present analyses.

**RESULTS** — The odds ratios (95% CI) for type 2 diabetes, after adjusting age, sex, BMI, family history of diabetes, and socioeconomic status, were 2.91 (1.25–6.76) for children with low birth weight (<2,500 g) and 1.78 (1.04–3.06) for those with high birth weight (≥4,000 g) when compared with the referent group (birth weight 3,000–3,499 g). The risk of diabetes was still 64% higher in the high birth weight group [odds ratio (OR) 1.64 (95% CI 0.91–2.96)], even after adjustment for gestational diabetes mellitus (GDM). Patients with type 2 diabetes who were born with high birth weight were more likely to have a higher BMI and diastolic blood pressure as well as a higher family history of diabetes compared with those with low birth weight.

**CONCLUSIONS** — A U-shaped relationship between birth weight and risk of type 2 diabetes was found in the schoolchildren aged 6–18 years in Taiwan. Schoolchildren with type 2 diabetes who were born with low birth weight had different metabolic phenotypes compared with those born with high birth weight.

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Interactions between fetal growth in utero and early postnatal environmental exposures have been considered pivotal to the manifestation of diabetes in later life (1–4). Such early adaptations to a nutritional environment might lead to a permanent change in the physiology of fuel metabolism and result in the expression of metabolic disturbances in adults, a process termed "metabolic programming" (5,6). Several epidemiological studies (7–12) suggest that, for both men and women, those born with low birth weight were at an elevated risk for type 2 diabetes and other health outcomes during adulthood. Initial observation was made from a follow-up study in Hertfordshire, U.K., to show the prevalence of impaired glucose tolerance or type 2 diabetes at age 64 years was inversely associated with birth weight (7). Despite the strength of association, currently all published studies have showed consistent results. Similar observations were recently seen in children and young adolescents (13–16).

Interestingly, studies in Pima Indians revealed a U-shaped relationship between birth weight and risk of type 2 diabetes (11). However, this relationship has not been found in other ethnic populations. This discrepancy has been attributed to a very high frequency of diabetes in Pima Indians, and therefore, gestational diabetes mellitus (GDM) is relatively common. Evidence suggests that the offspring of diabetic mothers are at higher risk for diabetes, an effect probably stemming from the influence of maternal diabetes (17–19). Because GDM is frequently complicated with macrosomia (20), a link between high birth weight and risk of diabetes can be anticipated. However, in a large study, the Nurses' Health Study, the risk of type 2 diabetes suggested a reverse J shape. These data stress the importance to elucidate pathophysiology of prenatal nutrition and other intrauterine environmental factors and the risk for type 2 diabetes in each of the different populations.

An increasing prevalence of childhood and adolescent type 2 diabetes has been identified during the past decades (21). One study (22) conducted in a large diabetes clinic in the midwestern U.S. demonstrated that type 2 diabetes accounted for 33% of all newly diagnosed diabetics aged 10–19 years in 1994. Type 2 diabetes has also become an epidemic in

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**Abbreviations:** ADA, American Diabetes Association; CFH, Chinese Foundation of Health; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HNF, hepatocyte nuclear factor; IFG, impaired fasting glycemia; NFG, normal fasting glycemia; OR, odds ratio; SBP, systolic blood pressure; SES, socioeconomic status.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Asian countries. In Japan, the incidence of type 2 diabetes is estimated to be ~2.8–4.6 per 100,000 children per year (23–25). In Taiwan, with the advent of a nationwide mass urine screening program for diabetes in schoolchildren in the past decade, we recruited a cohort of 1,966 subjects with diabetes and 96,548 subjects with normal fasting glycemia (NFG). In this study, we attempted to explore the relationship between birth weight and development of type 2 diabetes and other metabolic phenotypes among schoolchildren and adolescents aged 6–18 years via a national registry of birth weight (Taiwan's Birth Registry).

## RESEARCH DESIGN AND METHODS

From 1992 to 1997, a mass screening program for detecting diabetes and renal disease had been conducted in Taiwan, including all 21 counties and cities except the city of Taipei. All schoolchildren (~3,000,000 for each semester) from grades 1 to 12, aged 6–18 years, underwent urine screening each semester. This program was conducted by the Chinese Foundation of Health (CFH) with the support from the Taiwan Provincial Department of Health and the approval from the Provincial Education Board of Taiwan.

With consent and assistance obtained from the parents, nearly all of the students (average response rate 97%) were instructed to collect a midstream sample of the first morning urine. After glucosuria was confirmed in two sequential urine samples within 2 weeks, a third appointment was arranged for physical examination and collection of a fasting blood sample for determination of glucose and cholesterol levels. All blood samples were transferred to the central laboratory at the CFH headquarters. Blood glucose levels were measured by an automatic analyzer (Technican RA 2000 Serum Autoanalyzer; Bayer Diagnostic, Tarrytown, NY). For quality control, CFH participated in the College of American Pathologists quality assurance program and won a Good Performance award. According to 1997 American Diabetes Association (ADA) recommendations (26), subjects were classified into three categories, i.e., diabetes, impaired fasting glycemia (IFG), and NFG, based on fasting plasma glucose (FPG) levels. These students were referred for further diagnosis and care.

During this period (1992–1997), a total of 1,966 cases of diabetes were identified using the 1997 ADA criteria. For comparison, 1,780 control subjects were randomly selected from all students with NFG ($n$ = 96,548). All students with abnormal FPG were referred for clinical diagnosis; however, there was no evidence of the classification of diabetes by their physicians. To obtain further information to classify diabetes, we performed telephone questionnaire interviews with the students' parents regarding current weight and height, parental education years, age at diagnosis of diabetes, modalities of diabetes therapy (diet alone, antidiabetic oral medication, or insulin), interval between diagnosis (screening) and initiation of insulin treatment, and family history of diabetes and hypertension in first-degree relatives. Subjects were considered to have type 2 diabetes if both of the following criteria were met: *1*) FPG ≧126 mg/dl at screening; and *2*) current treatment with an oral hypoglycemic drug or diet control. Subjects who had received insulin injection within 3 years after diagnosis of diabetes were excluded from the study due to a possible diagnosis of type 1 diabetes or slowly progressive type 1 diabetes.

Data on birth weight and gestational age in weeks were obtained by matching the citizenship identification numbers with Taiwan's Birth Registry, Department of Internal Affairs, Executive Yuan, Republic of China.

### Statistical analysis

Descriptive data were shown as means and SDs for a continuous variable, and Student's $t$ test and $\chi^2$ test were used for assessing the differences between type 2 diabetes and NFG (Table 1). Birth weight was classified into five categories: <2,500, 2,500–2,999, 3,000–3,499,

**Table 1—*Demographic and anthropometric characteristics of the subjects with type 2 diabetes and NFG***

| | Boys | | Girls | |
|---|---|---|---|---|
| | T2D | NFG | T2D | NFG |
| *n* | 198 | 213 | 231 | 336 |
| Age (years) | 13.5 ± 2.4 | 13.5 ± 2.8 | 13.3 ± 2.5 | 13.1 ± 2.6 |
| Birth weight (g) | 3,374 ± 655 | 3,348 ± 473 | 3,404 ± 641 | 3,252 ± 437* |
| Gestation weeks | 39.7 ± 1.4 | 39.7 ± 1.2 | 39.7 ± 1.6 | 39.9 ± 0.9 |
| SBP (mmHg) | 119 ± 18 | 112 ± 14* | 117 ± 17 | 106 ± 12* |
| DBP (mmHg) | 73 ± 12 | 69 ± 10* | 74 ± 12 | 67 ± 9* |
| BMI (kg/m$^2$) | 24.5 ± 7.4 | 19.3 ± 3.2* | 24.9 ± 6.7 | 18.8 ± 3.3* |
| Obesity (%) | 42.2 | 6.6* | 49.3 | 3.6* |
| Positive family history of diabetes | 58.2 | 36.3* | 64.2 | 35.6* |
| Maternal age (years) | 26.1 ± 4.2 | 26.1 ± 3.9 | 25.9 ± 5.0 | 25.6 ± 4.0 |
| Paternal age (years) | 29.9 ± 5.6 | 29.0 ± 5.1 | 29.5 ± 5.6 | 28.9 ± 4.7 |
| Maternal BMI (kg/m$^2$) | 23.9 ± 3.6 | 23.2 ± 3.0* | 24.7 ± 4.0 | 23.0 ± 3.3* |
| Paternal BMI (kg/m$^2$) | 24.4 ± 3.1 | 24.1 ± 3.8 | 25.0 ± 3.8 | 24.3 ± 3.2* |
| SES | | | | |
| Low | 88 (38.8) | 72 (30.9) | 102 (39.1) | 113 (30.8) |
| Middle | 109 (48.0) | 124 (53.2) | 132 (50.6) | 203 (55.3) |
| High | 30 (13.2) | 37 (15.9) | 27 (10.3) | 51 (13.9) |

Data are means ± SD or *n* (%) unless otherwise indicated. *$P$ value <0.05 (T2D versus NFG). T2D, type 2 diabetes.

**Table 2—*OR for type 2 diabetes by birth weight category in the schoolchildren in Taiwan***

| Variable | Birth weight (g) category | | | | |
|---|---|---|---|---|---|
| | <2,500 | 2,500–2,999 | 3,000–3,499 | 3,500–3,999 | ≥4,000 |
| *n* (case/control) | 23/17 | 71/90 | 153/262 | 115/137 | 67/43 |
| Crude OR | 2.32 (1.20–4.47) | 1.35 (0.93–1.96) | 1.00 | 1.43 (1.05–1.98) | 2.67 (1.73–4.11) |
| OR (95% CI of diabetes) after adjustment for: | | | | | |
| Age | 2.30 (1.19–4.44) | 1.34 (0.93–1.95) | 1.00 | 1.42 (1.04–1.96) | 2.67 (1.73–4.11) |
| Age and sex | 2.27 (1.17–4.39) | 1.35 (0.93–1.95) | 1.00 | 1.42 (1.03–1.96) | 2.61 (1.69–4.02) |
| Age, sex, and BMI | 2.38 (1.12–5.06) | 1.47 (0.94–2.29) | 1.00 | 1.30 (0.89–1.90) | 2.06 (1.25–3.40) |
| Age, sex, BMI, and family history of diabetes | 2.17 (1.00–4.75) | 1.41 (0.89–2.22) | 1.00 | 1.15 (0.77–1.72) | 1.79 (1.06–3.02) |
| Age, sex, BMI, family history of diabetes, and SES | 2.91 (1.25–6.76) | 1.41 (0.89–2.25) | 1.00 | 1.19 (0.79–1.78) | 1.78 (1.04–3.06) |
| Age, sex, BMI, family history of diabetes, SES, and GDM | 2.87 (1.19–6.92) | 1.46 (0.90–2.38) | 1.00 | 1.18 (0.76–1.83) | 1.64 (0.91–2.96) |

3,500–3,999, and ≥4,000 g. Test for linear trend based on linear regression with adjustment for age and sex (and height for blood pressure) was derived for comparisons of selected variables in type 2 diabetes by birth weight categories. Linear regression and multivariate logistic regression adjusted age and sex (and height for blood pressure) were used for testing significance between the low birth weight (<2,500 g) and high birth weight (≧4,000 g) subjects with type 2 diabetes as well. Odds ratio (OR) and 95% CI were calculated to estimate the relative risk of type 2 diabetes by birth weight category using those of 3,000–3,499 g as the referent group (OR = 1) in the multivariate logistic regression model. Age, sex, BMI, family history of diabetes (in their first-degree relatives), socioeconomic status (SES), and GDM were potential covariates and were adjusted in different models of analyses. Parental education levels (≦9, 10–12, and ≧13 years of education) were used as the indicator of SES in our present study. Obesity was defined for students as BMI ≧95th percentile of the sex- and age-specific anthropometry of the children in Taiwan (27). All statistical analyses were performed with SPSS statistical software package (version 10.0; SPSS, Chicago, IL). A $P$ value <0.05 was considered statistically significant.

**RESULTS** — Among 1,966 subjects with diabetes and 1,780 subjects of NFG, 825 of those with diabetes (42%) and 673 of those with NFG (38%) were successfully traced by telephone interviews. Because of incorrect or missing telephone numbers and addresses, the actual response rates were 86.5% for subjects with diabetes and 87.5% for those with NFG. There was no significant difference in terms of response rates between participants and nonparticipants with respect to age and sex at screening. After excluding subjects with type 1 diabetes ($n$ = 330) and those with missing data on birth weight ($n$ = 146), our analysis was confined to 978 participants (429 with type 2 diabetes and 549 with NFG).

As shown in the Table 1, there were no significant differences in the distribution of age, gestation weeks, and SES between the subjects with type 2 diabetes and NFG. However, subjects with type 2 diabetes were associated with a significantly higher level of BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), and family history of diabetes in first-degree relatives (all the $P$ values were <0.05 for both boys and girls). Using BMI ≧95th percentile for age- and sex-matched values of the anthropometry in Taiwan (27) to define obesity, the rate of obesity was much higher for students with type 2 diabetes than students with NFG: 42.2 vs. 6.6% for boys and 49.3 vs. 3.6% for girls. Interestingly, maternal BMI consistently showed a significant difference between the subjects with type 2 diabetes and NFG. There was no significant difference in SES between type 2 diabetes and NFG.

To assess the relation of birth weight and the risk of type 2 diabetes in our cohort, multivariate logistic regression was applied in different models (Table 2). A U-shaped relationship was initially observed for the crude risk of developing type 2 diabetes across different birth weight categories (Table 2 and Fig. 1). After adjusting for age, sex, BMI, family history of diabetes, and SES in different models, the risk of type 2 diabetes remained significantly high for the low birth weight (<2,500 g) and high birth weight groups (≧4,000 g) as compared with the referent group (Table 2). In contrast to the low birth weight group, the odds for type 2 diabetes were reduced when adjusted with the confounding factors and to a nonsignificant level after adjustment with GDM in the high birth weight group (Fig. 1).

To compare clinical characteristics among the subjects with type 2 diabetes born with low or high birth weight, a linear regression was applied to test the $P$ for trends across five different birth weight categories and multivariate logistic regression adjusted with age and sex were used for testing significance between type 2 diabetes subjects with low birth weight (<2,500 g) and high birth weight (≧4,000 g) (Table 3). As can be seen, type 2 diabetic subjects born with high birth weight had higher BMI and DBP as well as a higher incidence of family history of diabetes compared with type 2 diabetic subjects born with low birth weight.

**CONCLUSIONS** — In the present study, we analyzed the impact of birth weight on various metabolic phenotypes in a young cohort aged 6–18 years based on a nationwide screening program from 1992 to 1997. We first confirmed a U-

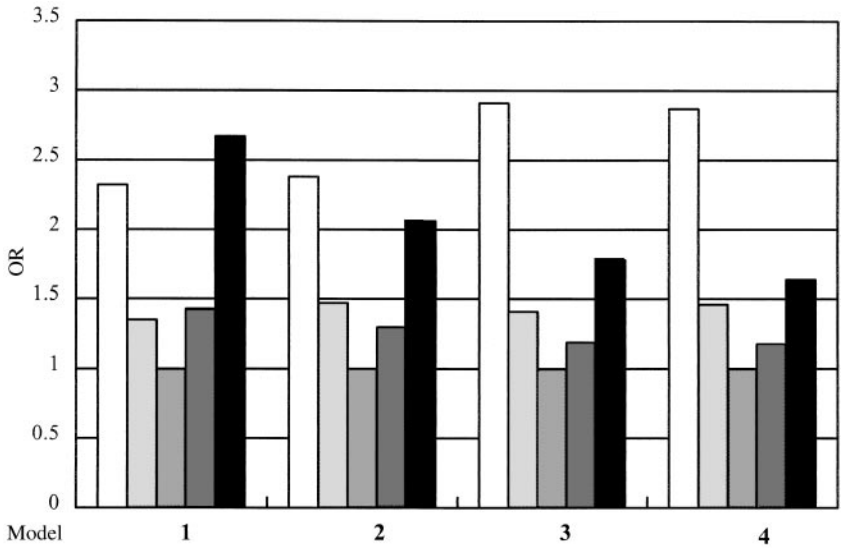


**Figure 1—***ORs for type 2 diabetes in schoolchildren by birth weight categories. ORs were calculated to estimate the relative risk of type 2 diabetes by birth weight category using subjects with birth weight of 3,000–3,499 g as the referent group (OR = 1) in different multivariate logistic regression models, i.e., crude OR without adjustment (model 1), and adjusted for age, sex, and BMI (model 2), further adjusted for family history of diabetes and SES (model 3), and together with GDM (model 4). Different birth weight categories are shown in vertical bars with a 500-g increment in birth weight from <2,500 (white bar) to >4,000 g (black bar).*

shaped relation between birth weight and the risk of type 2 diabetes, which was originally demonstrated in children and young adults in a study of Pima Indians (28). In the type 2 diabetic subjects born with high birth weight, blood pressure was higher, BMI was greater, and the incidence of positive family history of diabetes was higher than in those born with low birth weight, indicating a possibility of a different pathogenesis of type 2 diabetes in subjects with low and high birth weight. The constellation of diabetes, obesity, and high blood pressure, collectively termed metabolic syndrome, was more frequently observed in the subjects born with high birth weight.

The discovery that childhood type 2 diabetes is associated with obesity in the present study was consistent with previous reports (12,29,30). It is well known that obesity is an important risk factor for type 2 diabetes (31–33). However, a significant linear and positive trend for BMI across different birth weight categories was found in type 2 diabetes. After adjustment with age, sex, and current BMI, subjects born with the lowest (<2,500 g) and highest (≧4,000 g) birth weight were still at significant risk for type 2 diabetes when compared with the referent group (birth weight 3,000–3,500 g). These results suggest that both current BMI and birth weight are independent risk factors for development of type 2 diabetes. Indeed, adults born with low birth weight and having a high current BMI were shown to be more insulin resistant (34,35) and at the highest risk for type 2 diabetes (7). These observations might also be true in childhood (16). In contrast to the observation in other reports, including a recent study (36) showing that the U-shaped relation was converted to a reverse J shape after adjustment for history of maternal diabetes, the U-shaped curve persisted, with a 64% excess risk in those with high birth weight in our study population. Although the significance was slightly reduced after adjustment for GDM, it is anticipated due to a tight correlation between GDM and macrosomia. This suggests that, at least in this population, factors other than maternal diabetes contribute to the high risk of diabetes among babies with high birth weight.

Previous studies suggested that a defect in insulin sensitivity (37) and deficient pancreatic β-cell function (4) might be associated with subjects with low birth weight, independent of current BMI. Whether these defects are inherited or acquired in utero or postnatally remain to be answered. There are some debates on the argument that genetic influences on birth weight (38) or an interaction between genetic and environmental effect might lead to development of type 2 diabetes for subjects with low birth weight (39). A recent search for candidate genes involved in fetal growth identified that glucokinase gene mutation resulted in re-

**Table 3—***Clinical characteristics of type 2 diabetes in schoolchildren by birth weight categories*

| | Birth weight (g) category | | | | |
|---|---|---|---|---|---|
| Variable | <2,500 | 2,500–2,999 | 3,000–3,499 | 3,500–3,999 | ≥4,000 |
| *n* (male/female) | 11/12 | 33/38 | 77/76 | 47/68 | 30/37 |
| Gestation weeks | 36.8 ± 3.7 | 39.6 ± 1.4 | 39.9 ± 1.0 | 39.9 ± 0.7 | 39.8 ± 1.1* |
| BMI (kg/m$^2$) | 23.9 ± 5.8 | 23.6 ± 7.1 | 24.8 ± 7.8 | 24.9 ± 6.7 | 25.6 ± 5.9* |
| SBP (mmHg) | 113 ± 14 | 118 ± 19 | 119 ± 19 | 118 ± 18 | 119 ± 15 |
| DBP (mmHg) | 70 ± 12 | 72 ± 12 | 73 ± 12 | 76 ± 11 | 75 ± 12† |
| Obesity rates (%) | 38.1 | 35.9 | 51.4 | 43.1 | 51.6 |
| Family history of diabetes (%) | 59.1 | 58.8 | 51.0 | 65.4 | 84.8‡ |

Data are means ± SD unless otherwise indicated. *$P < 0.05$ for trend derived by linear regression adjusted with age and sex by birth weight categories; †$P < 0.05$ for trend derived by linear regression adjusted with age, sex, and height by birth weight categories; ‡*P* value ≤0.05 between low and high birth weight was derived by linear regression adjusted for age and sex.

duced birth weight (40,41). Other genes, such as insulin receptor substrate-1, hepatocyte nuclear factor-1α (HNF-1α), HNF-4α, and HNF-6 had been excluded as major genes for controlling birth weight (42). In our present analysis, even after adjusting for age, sex, BMI, family history of diabetes, and SES, both low and high birth weight remained a significant risk factor for type 2 diabetes. However, the risk was reduced to a nonsignificant level in the subjects with high birth weight after adjustment for maternal history of GDM. Our findings strongly support an independent effect of reduced fetal growth (more environmental effect) on the outcome of diabetes, but it might be linked to some genetic factors inherited in those with high birth weight, because the percentage of maternal GDM and the positive family history of diabetes in their first-degree relatives was higher in subjects with type 2 diabetes born with high birth weight.

Low birth weight has been linked to development of hypertension in adult life (43). On the contrary, the present study demonstrates an increase in DBP with increasing birth weight in children with type 2 diabetes. Therefore, it is speculative that a heterogeneity of pathogenesis exists among the subjects with type 2 diabetes born with a low or high birth weight; namely, those born with a high birth weight are more similar to subjects with adult metabolic syndrome. However, we cannot exclude the possibility of an age-dependent effect on clinical manifestations or mechanisms other than insulin resistance in the pathogenesis of type 2 diabetes, obesity, and essential hypertension.

Differentiating between type 1 diabetes or type 2 diabetes in childhood is very difficult, even in a clinical setting. In this study, there was a limitation in classification of type 1 diabetes and type 2 diabetes because the ascertainment of type 2 diabetes was based on questionnaire interviews. Although misclassifications may occur, the validity of self-reported type 2 diabetes has been documented in the Nurses' Study (44), in which 98% of the cases could be confirmed by reviewing medical records. Because all students with the disease were under medical care with a clinical diagnosis (either type 1 diabetes or type 2 diabetes) and the lack of information in disease type was not included in this study, the classification of type 1 diabetes and type 2 diabetes should be acceptable in this nationwide epidemiological study.

In summary, a U-shaped relationship between birth weight and risk of type 2 diabetes was confirmed in our population, as demonstrated by the Pima Indians. Our findings support an independent role of birth weight on development of type 2 diabetes in addition to sex, age, BMI, positive family history of diabetes, and SES. Subjects with type 2 diabetes born with high birth weight tended to have higher BMI and DBP than those with low birth weight.

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