The association between birth weight and the risk of type 2 diabetes mellitus: a systematic review and meta-analysis

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Abstract. Previous studies have shown a relationship between type 2 diabetes mellitus and birth weight. We performed this meta-analysis to resolve the problem of inconsistent results. We conducted a literature search of PubMed, Embase and the Cochrane Library using “Diabetes Mellitus, Type 2,” “Birth Weight,” and some related free words. Twenty-one studies were included in accordance with inclusion and exclusion criteria, involving a total of 313,165 participants and 22,341 type 2 diabetes mellitus cases. A modified version of the Newcastle-Ottawa Scale was used to evaluate the methodological quality of studies included. We used Review Manager 5.3 for data merging and statistical analysis. Results were expressed as odds ratio (OR) and 95% confidence interval (95% CI). The risk of diabetes with low birth weight (<2,500 g) was higher than that with birth weight ≥2,500 g, (OR = 1.51, 95% CI: 1.43, 1.58). Compared with normal birth weight (2,500–4,000 g), low birth weight, but not high birth weight, increased the risk of diabetes (OR = 1.41, 95% CI: 1.26, 1.58). There is a negative association between birth weight and the future risk of type 2 diabetes mellitus.

Key words: Diabetes mellitus, Type 2, Birth weight, Meta-analysis

DIABETES MELLITUS, a metabolic disease, is a major health problem worldwide. In 2013, 382 million people were suffering from diabetes, and it is estimated that the number of individuals with diabetes will increase to 592 million by 2035 [1]. Diabetes complications and an increasing mortality rate have also attracted the attention of clinical researchers.

It has been confirmed by many studies that birth weight (BW) is associated with the onset of diabetes. Some studies found that low birth weight (LBW) increases the risk of type 2 diabetes mellitus (T2DM), whereas Lammi [2] and Dyck [3] suggested that neonates with high birth weight (HBW) are more likely to develop diabetes as adults. Gestational diabetes mellitus (GDM) and weight gain during pregnancy or obesity are likely factors affecting fetal BW [4]. Observational studies usually exclude mothers with GDM, thereby reducing the proportion of the population with HBW. Women who are obese and suffer from GDM usually have HBW owing to increased body fat rather than lean weight gain [5]. Infants whose mothers have GDM are characterized by higher weight for the concomitant gestational age, or macrosomia [6]. Macrosomia might be a reflection of overweight mothers, mothers with GDM, or extended pregnancy. In addition, other studies [7, 8] have concluded that only individuals with a normal BW have a relatively low risk of diabetes. Historically, differences exist...
with regard to type and year of experiment, race, population, geographic region, and so forth, leading to varying results to some extent. In 2007 and 2008, Harder and Whincup suggested a U-shaped and linear inverse relationship between BW and the risk of T2DM.

In view of the inconsistencies of individual studies and the differences in the results of the two meta-analyses thus far published, we performed a meta-analysis focusing on more recent research that has emerged from 2008 to 2018 to elucidate the relationship between BW and the risk of T2DM.

Materials and Methods

Search strategy
We searched PubMed, Embase and the Cochrane Library for relevant articles without date limitations. The main search terms used were key words “Diabetes Mellitus, Type 2” and “Birth Weight,” and some related free words, such as “Diabetes Mellitus, Noninsulin-Dependent,” “Diabetes Mellitus, Ketosis-Resistant,” “Diabetes Mellitus, Stable,” “Maturity-Onset Diabetes Mellitus,” “Birth Weights,” and “Weight, Birth.” The searches were limited to peer-reviewed studies in the English language. The references in relevant articles and reviews were also checked to avoid overlooking any studies. The search strategy is described in Supplementary Material 1.

Inclusion and exclusion criteria
Included studies had to meet the following criteria: (i) cohort or case-control study; (ii) the literature covers BW and T2DM; (iii) the literature contains at least one of the following groups: LBW, <2,500 g; NBW, 2,500–4,000 g; HBW, >4,000 g; (iv) the original data could be obtained directly or through data conversion.

Exclusion criteria were as follows: (i) Review, case report, comment, animal research, cell research; (ii) Type 1 diabetes and other types of diabetes; (iii) Literature is incomplete, a repeated publication, or of poor quality; (iv) Literature involved gestational diabetes mellitus and offspring BW; (v) The article studies the relationship between mother (or father) with diabetes and the BW of the next generation.

Data extraction and quality evaluation
Two independent authors extracted the following information: first author, publication year, country, study design, year of birth, age, BW reference category, number of participants, number of T2DM, confounding factors, rate of loss to follow-up, and relationship between BW and T2DM.

A modified version of the Newcastle-Ottawa Scale (NOS; see Supplementary Material 2) was used to evaluate the methodological quality of studies included in this review. The NOS consists of three parts: selection (0–4 points), comparability (0–2 points), and exposure (or outcome assessment) (0–3 points). Scores of 7–9 were classified as high-quality studies, 4–6 as moderate-quality studies, and 0–3 as low-quality studies. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Statistical analysis
We used Review Manager 5.3 for data merging and statistical analysis. The statistical model is based on Mantel-Haenszel, the effect index is Odds Ratio (OR) with 95% confidence interval (95% CI), and the analysis model is the fixed-effects model. The heterogeneity test was performed according to the $I^2$ value and Q value statistical tests. No heterogeneity, $0 \leq I^2 < 25$%; mild heterogeneity, $25 \leq I^2 < 50$; moderate heterogeneity, $50 \leq I^2 < 75$; severe heterogeneity, $\geq 75$%. If there was obvious heterogeneity, we tried to find out the source by sensitivity analysis and subgroup analysis. We deleted each of the articles to discern whether there was a significant change in the heterogeneity upon sensitivity analysis. If not, the article was deemed not to be the source of heterogeneity. Subgroup analysis is described below.

Results

Literature search
A total of 2,339 studies were retrieved through the search of the databases. Ultimately, 18 articles met the inclusion criteria and were included in the meta-analysis (Flow chart shown in Fig. 1).

Study characteristics
A total of 313,165 participants and 22,341 T2DM cases were involved from 21 studies, which included 17 cohort studies and 4 case-control studies. Among these studies, 12 showed an inverse linear association between BW and T2DM, 2 concluded that there were positive associations, 3 revealed a U-shaped association, 3 showed unrelated associations, and 1 study showed a difference according to sex. The information we extracted from the articles is shown in Tables 1, 2 and 3.
The risk of diabetes in newborns <2,500 g and ≥2,500 g

Fig. 2 is a forest plot showing that the risk of diabetes with LBW (<2,500 g) was higher than that in neonates ≥2,500 g. (OR = 1.51, 95% CI: 1.43, 1.58). There was moderate heterogeneity (Q value test $p < 0.1$, $I^2 = 71\%$) among the 17 studies included. Despite subgroup analyses conducted according to the age, type of study, publication time, race, rate of loss to follow-up and World War II time, we did not find the source of heterogeneity. A subsequent sensitivity analysis revealed no significant heterogeneity. A funnel chart (Fig. 3) was used to evaluate publication bias, whereby the symmetry was poor, suggesting a certain degree of publication bias.

**The risk of diabetes in newborns <2,500 g and ≥2,500 g**

Fig. 2 is a forest plot showing that the risk of diabetes with LBW (<2,500 g) was higher than that in neonates ≥2,500 g. (OR = 1.51, 95% CI: 1.43, 1.58). There was moderate heterogeneity (Q value test $p < 0.1$, $I^2 = 71\%$) among the 17 studies included. Despite subgroup analyses conducted according to the age, type of study, publication time, race, rate of loss to follow-up and World War II time, we did not find the source of heterogeneity. A subsequent sensitivity analysis revealed no significant heterogeneity. A funnel chart (Fig. 3) was used to evaluate publication bias, whereby the symmetry was poor, suggesting a certain degree of publication bias.

**Table 1** Main characteristics of all the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication year</th>
<th>Country</th>
<th>Study design</th>
<th>Year of birth</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyck [3] (I)</td>
<td>2001</td>
<td>Canada</td>
<td>Case-control study</td>
<td>1950–1984</td>
<td>10.5–44.9</td>
</tr>
<tr>
<td>Dyck [3] (II)</td>
<td>2001</td>
<td>Canada</td>
<td>Case-control study</td>
<td>1950–1984</td>
<td>10.5–44.9</td>
</tr>
<tr>
<td>Jornayvaz [16]</td>
<td>2016</td>
<td>Switzerland</td>
<td>Cohort Study</td>
<td>1928–1971</td>
<td>35–75</td>
</tr>
<tr>
<td>Li [17] (I)</td>
<td>2015</td>
<td>America</td>
<td>Cohort Study</td>
<td>1931–1936 approximately 50–55</td>
<td></td>
</tr>
<tr>
<td>Li [17] (II)</td>
<td>2015</td>
<td>America</td>
<td>Cohort Study</td>
<td>1928–1931</td>
<td>45–48</td>
</tr>
<tr>
<td>Li [17] (III)</td>
<td>2015</td>
<td>America</td>
<td>Cohort Study</td>
<td>1954–1956</td>
<td>35–37</td>
</tr>
<tr>
<td>Xiao [22]</td>
<td>2008</td>
<td>China</td>
<td>Case-control study</td>
<td>1921–1954</td>
<td>49–84</td>
</tr>
<tr>
<td>Young [23]</td>
<td>2002</td>
<td>Canada</td>
<td>Case-control study</td>
<td>&gt;1984</td>
<td>&lt;18</td>
</tr>
</tbody>
</table>

**Fig. 1** Flow chart of included studies.

**The risk of diabetes in newborns <2,500 g and ≥2,500 g**

Fig. 2 is a forest plot showing that the risk of diabetes with LBW (<2,500 g) was higher than that in neonates ≥2,500 g. (OR = 1.51, 95% CI: 1.43, 1.58). There was moderate heterogeneity (Q value test $p < 0.1$, $I^2 = 71\%$) among the 17 studies included. Despite subgroup analyses conducted according to the age, type of study, publication time, race, rate of loss to follow-up and World War II time, we did not find the source of heterogeneity. A subsequent sensitivity analysis revealed no significant heterogeneity. A funnel chart (Fig. 3) was used to evaluate publication bias, whereby the symmetry was poor, suggesting a certain degree of publication bias.

The risk of diabetes in newborns <2,500 g and 2,500–4,000 g

The risk of diabetes in subjects with LBW was 0.41 times higher than that in the NBW group (OR = 1.41, 95% CI: 1.26, 1.58). $p > 0.1$ with $I^2 = 33\%$ was considered homogeneous among the 7 studies included (Fig. 4). The funnel chart (Fig. 5) showed that the publication bias was minor.
The risk of diabetes in newborns >4,000 g and 2,500–4,000 g

Using 2,500–4,000 g as the reference weight, the risk of diabetes in neonates with HBW did not increase (OR = 1.11, 95% CI: 1.00, 1.24) (Fig. 6). Given the heterogeneity test values $I^2 = 82\%$ and $p < 0.1$, a subgroup analysis was conducted. The $I^2$ values were 17% and 44% in the case-control study group and cohort study group, respectively ($p > 0.1$); therefore, the source of heterogeneity was the type of study. The publication bias was not obvious (Fig. 7).

**Discussion**

The classification of BW is not consistent across the published articles on infant BW and diabetes risk. For example, the BW unit was “pound” (lb) in Rich-Edwards’ article [24], whereas Zimmermann [25] divided BW into 2,000–2,750 g, 2,751–3,250 g, 3,251–3,750 g, and so forth. Moreover, weight values were not the same after conversion. These differences resulted in a limited number of articles being included. Weight grouping may be based on research design or national habits, and the literature included in this analysis applied a classification that is internationally recognized and commonly used, namely LBW <2,500 g, NBW 2,500–4,000 g, and HBW >4,000 g. In this meta-analysis, BW was first divided into <2,500 g and ≥2,500 g; the data were then collected to investigate whether the future risk of diabetes with LBW would increase. Next, BW was divided into <2,500 g, 2,500–4,000 g, and >4,000 g to determine which group would carry an increased risk of diabetes.

Compared with BW ≥2,500 g, the subjects with BW

**Table 2** Main characteristics of all the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Number of participants</th>
<th>Number of T2DM</th>
<th>Confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker</td>
<td>13,517</td>
<td>698</td>
<td>Year of birth, sex</td>
</tr>
<tr>
<td>Dyck (I)</td>
<td>1,728</td>
<td>846</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Dyck (II)</td>
<td>2,264</td>
<td>1,164</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Erikson</td>
<td>8,702</td>
<td>290</td>
<td>/</td>
</tr>
<tr>
<td>Fall</td>
<td>501</td>
<td>75</td>
<td>Age, sex, BMI</td>
</tr>
<tr>
<td>Forien</td>
<td>7,044</td>
<td>741</td>
<td>Weigh at age 7 years</td>
</tr>
<tr>
<td>Guillain</td>
<td>77,496</td>
<td>1,871</td>
<td>Year of birth, physical activity, preterm birth history, family history of diabetes</td>
</tr>
<tr>
<td>Hjort</td>
<td>953</td>
<td>350</td>
<td>Age, sex, BMI, family history of diabetes, social status, gestational diabetes</td>
</tr>
<tr>
<td>Johansson</td>
<td>18,230</td>
<td>592</td>
<td>/</td>
</tr>
<tr>
<td>Jornayvaz</td>
<td>2,546</td>
<td>111</td>
<td>/</td>
</tr>
<tr>
<td>Li (I)</td>
<td>18,305</td>
<td>1,603</td>
<td>Age, BMI, ethnicity, marriage, social status, living condition</td>
</tr>
<tr>
<td>Li (II)</td>
<td>49,757</td>
<td>5,381</td>
<td>Age, BMI, ethnicity, marriage, social status, living condition</td>
</tr>
<tr>
<td>Li (III)</td>
<td>81,732</td>
<td>4,725</td>
<td>Age, BMI, ethnicity, marriage, social status, living condition</td>
</tr>
<tr>
<td>Maahs</td>
<td>3,714</td>
<td>354</td>
<td>/</td>
</tr>
<tr>
<td>McCane</td>
<td>1,179</td>
<td>210</td>
<td>Age</td>
</tr>
<tr>
<td>Ruiz-Narváez</td>
<td>21,624</td>
<td>2,388</td>
<td>Age, family history of diabetes, calorie intake, physical activity</td>
</tr>
<tr>
<td>Veena</td>
<td>487</td>
<td>20</td>
<td>Age, sex, BMI</td>
</tr>
<tr>
<td>Veena</td>
<td>266</td>
<td>56</td>
<td>Age, sex, BMI</td>
</tr>
<tr>
<td>Wei</td>
<td>978</td>
<td>429</td>
<td>Age, sex, BMI, family history of diabetes</td>
</tr>
<tr>
<td>Xiao</td>
<td>2,004</td>
<td>391</td>
<td>/</td>
</tr>
<tr>
<td>Young</td>
<td>138</td>
<td>46</td>
<td>Diabetes during pregnancy, diet, smoking and drinking during pregnancy, breastfeeding, mother’s pregnancy BMI</td>
</tr>
</tbody>
</table>
<2,500 g had a 0.51-fold increased risk of diabetes, and the results showed moderate heterogeneity. The source of heterogeneity was not detected in the subgroup or sensitivity analyses. Given the differences in age, study design, publication time, race, follow-up time, and so forth, heterogeneity might be involved in many aspects. Some literature supports that before, during and after World War II, people’s living environment changed, especially nutrition, affecting metabolism and related diseases [26]. We performed subgroup analyses of two scenarios (>4,000 g vs. 2,500–4,000 g and <2,500 g vs. ≥2,500 g) involving studies from a range of time periods, including World War II (1939–1945), but World War II was not source of heterogeneity in these analyses. Using the NBW of 2,500–4,000 g as a reference, the results show that the risk of diabetes increases with LBW, but not with HBW, indicating a negative association between BW and diabetes risk. Genetic correlation analysis is less affected by confounding factors and is increasingly being used to analyze causality. A genome-wide association study of 69,308 European pedigrees found that there was a causal link between LBW and an increased risk of T2DM [27]. One study found that LBW rather than HBW was associated with T2DM risk factors such as fasting blood glucose, fasting insulin, and insulin resistance index levels among 10,758 children and adolescents aged 6–15 years [28]. Weight is an indicator of nutritional status, but not specific factors that are more susceptible to late pregnancy growth [29]. LBW is an indicator of intrauter-
ine malnutrition and growth restriction, which may induce pancreatic β-cell dysplasia, delay skeletal muscle development [30], and alter the hypothalamic-pituitary-adrenal axis set point as well as genetic or epigenetic changes [31]. Environmental factors that contribute to intrauterine malnutrition or reduce placental efficacy might lead to decreased fetal BW [32]. Fetal nutrition and growth potentially affect health in adulthood [33]. Fetal growth restriction can change the physiology and structure of the body, engendering increased risk of and susceptibility to diseases such as metabolic disorders in the future [34]. This aspect can be explained by epigenetics. DNA methylation is replicated by DNA methyltransferase 1 (DNMT1) during DNA replication, which means that environmental changes that occur during early development could be transferred to subsequent
cells by cell division. Therefore, changes in the fetal environment could alter the epigenetic genome of specific cells or tissues, thereby permanently altering the structure and (or) function of different organs [35]. Studies from the UK, China, and Ukraine showed that individuals with restricted intrauterine growth are more sensitive to hyperglycemia or T2DM [36-38]. An increased risk of T2DM in identical twins suggests that fetal nutrition plays a more important role than genetics [29].

In 1992, Hales and Barker proposed the “thrifty phenotype hypothesis” [39] (or fetal programming hypothesis), which is based on fetal malnutrition. This hypothesis suggests that as a result of malnutrition within the uterus, individual metabolic procedures are reprogrammed to become “nutrition thrifty.” Although the thrifty phenotype would confer a survival advantage under nutritional deficiency, rapid growth occurs and the body begins to store fat rather than muscle [40] in the case of improved nutrition, making it more prone to insulin resistance, T2DM, and other metabolic defects [41]. The risk of adult T2DM is significantly increased when the adaptive response to hunger in the fetus does not match subsequent improvement in the nutritional environment [42]. Fetal malnutrition could lead to a permanent change in glucose metabolism [39], although the underlying mechanism is unclear.

In addition to the fetal phenotype hypothesis, the fetal insulin hypothesis [43] also explains the relationship between LBW and T2DM. It is well known that insulin
is necessary for fetal growth. Hales and Barker suggested that β cells begin to appear in the fetus. The development of fetal pancreatic β cells and physiological function is affected by the lack of maternal amino acids [29]. The fetal insulin hypothesis states that LBW and T2DM might have a common genetic basis [27]. LBW and T2DM are different phenotypes of the same genotype, and the genetic variation that affects fetal pancreatic development would result in increased fetal growth resulting from a lack of insulin secretion, leading to an increased risk of T2DM [43]. Studies have found that three genetic loci associated with T2DM (ADCY5,
CDKAL1, and HHEX-IDE) are also related to LBW, and at least two loci (CDKAL1 and HHEX-IDE) are associated with β-cell dysfunction [27, 44].

Previous studies have shown that the relationship between LBW and the risk of T2DM is more pronounced among overweight adults: both BLW and overweight adults increase the risk by 40-fold. In three cohort studies by Li, the combination of LBW and adult lifestyle was associated with a risk of T2DM. The relationship between early-life exposure factors and subsequent metabolic diseases can be changed by adult lifestyles [23]. Therefore, it is important to emphasize the role of lifestyle changes in the prevention of T2DM. The simultaneous improvement of prenatal and postnatal factors could further prevent disease. LBW individuals could maintain glucose tolerance through regular physical exercise [45]. These findings suggest that prenatal malnourished fetuses might be more sensitive to unhealthy lifestyles in the future. From a public health viewpoint, susceptible persons could prevent diabetes by maintaining a healthy weight.

The NOS scale is used to evaluate the quality of the literatures in case-control or cohort studies. In accordance the actual situation, our analysis employed a certain modification. High-quality literature usually has longer follow-up or lower non-response rates, better representativeness of population selection, more confounding factors, and more objective BW records in comparison with moderate- and low-quality research. The case-control study is designed from the viewpoint of result deriving from cause, with no real observation of the process from cause to result. As it is retrospective and not in the chronological order cause-to-result, this leads to many opportunities for information bias to occur, so the ability of case-control studies to demonstrate a causal relationship is poor in comparison with cohorts. Causal hypothesis can be tested but cannot be confirmed in case-control studies. In a cohort study, the researcher realistically observes the process from cause to result. It is effective in demonstrating causation with high quality of evidence, and can confirm the causal hypothesis. In the literature included herein, BW was obtained in different ways. Some studies were based on birth records, while others were self-reported through memories, questionnaires, and so forth. As self-reported data are less reliable than those objectively gathered, the introduction of information bias is possible. Methods of recording BW constitute one aspect of quality assessment in the NOS.

Some limitations of our analysis should be acknowledged. First, not all available databases were searched and the literature was restricted to articles in English, leading to some studies being overlooked. Second, there was large heterogeneity of diabetes risk in newborns <2,500 g and ≥2,500 g. We performed subgroup analyses based on age, sex, study design and so forth, but could not find the source of this heterogeneity. Third, some BW measurements were not based on objective records but on the subjects’ memory, and thus were less accurate and reliable. The bias of such information can affect the outcomes of individual studies.

In conclusion, LBW is significantly associated with T2DM, while macrosomia is not. If we were able to determine the mechanisms that produce neonatal BW below the normal level and avoid BW of less than 2,500 g, the risk of T2DM would be reduced.

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