Birth weight and type 2 diabetes: A meta-analysis

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Abstract. The prevalence of T2DM is increasing around the world on a yearly basis. A meta-analysis was conducted to analyze the association between birth weight and incidence of type 2 diabetes mellitus (T2DM). A literature search was performed from January 1990 to June 2016 in PubMed, ScienceDirect, SpringerLink, China National Knowledge Infrastructure and Chinese Biomedical Literature Database. After reviewing characteristics of all the included studies systematically, a meta-analytical method was employed to calculate the pooled odds ratios (ORs) and associated 95% confidence intervals (CI) from random-effects models. Heterogeneity was assessed by Q-statistic test. Funnel plot, Begg's and Egger's linear regression tests were applied to evaluate publication bias. A sensitivity analysis was also performed to assess the robustness of results. According to inclusion and exclusion criteria, 8 studies were selected to be included in the meta-analysis. Compared with normal birth weight (2,500-4,000 g), low birth weight (<2,500 g) was associated with an increased risk of T2DM (OR, 1.55; 95% CI, 1.39-1.73; P<0.001). No significant difference was observed between high birth weight (>4,000 g) and normal birth weight in terms of the risk of T2DM (OR, 0.98; 95% CI, 0.79-1.22). Compared with high birth weight, low birth weight was associated with an increased risk of diabetes mellitus (OR, 1.58; 95% CI, 1.30-1.93; P<0.001). These findings indicated that there may be an inverse linear association between birth weight and T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is a common complex disease defined by hyperglycemia (1). The prevalence of T2DM is increasing year by year around the world and is becoming a serious global public health problem (1,2). However, identifying the pathogenesis and mechanism is difficult due to

heterogeneous phenotypes and a broad spectrum of pathophysiological processes (3). A previous study indicated that genetic variation and various postnatal factors (including smoking, physical activity and education) are associated with T2DM (4). However, A recent study reported that low birth weight, which reflects the intrauterine nutrient conditions, was associated with metabolic disorders after birth, such as obesity and insulin resistance (5). Low birth weight has also been demonstrated to be associated with adult cardiovascular disease and diabetes (6-10). The mechanism behind these associations is still unclear. One proposal is the fetal programming hypothesis: A lack of intrauterine nutrients causes a permanent metabolic shift towards insulin resistance to support brain glucose supply. After birth, the nutrient supply increases, which may lead to obesity and insulin resistance (5,11-15). An alternative proposal is the fetal insulin hypothesis, which suggests that common genetic variants decrease insulin secretion and cause low birth weight (16). The relationship between high birth weight and T2DM is not consistent. Some studies have demonstrated that birth weight is negatively associated with T2DM and high birth weight (>4,000 g) decreases the risk of T2DM (17-19). Other studies have reported that both high and low birth weight increase the risk of T2DM, and high birth weight is also a risk factor for T2DM (20-23).

In the present study, a meta-analysis was conducted in order to provide a comprehensive overview of the association between birth weight and T2DM.

Materials and methods

Search strategy. A literature search was conducted on PubMed (https://www.ncbi.nlm.nih.gov/pubmed), ScienceDirect (http://www.sciencedirect.com/), SpringerLink (https://link. springer.com/advanced-search), China National Knowledge Infrastructure (http://www.wanfangdata. com.cn/) and Chinese Biomedical Literature Database (http://www. sinomed.ac.cn/zh/) from January 1990 to June 2016 for relevant papers using the following terms: ˈbirth weight', ˈtype 2 diabetes', ˈnon-insulin-dependent', ˈNIDDM' and ˈrisk factor'. The articles were restricted to those written in English or Chinese. The reference lists of the retrieved articles were also manually reviewed to identify publications on the same topic.

Study selection. To qualify for the present meta-analysis, studies were required to meet the following criteria: i) Unrelated cohort study; ii) recruited sufficient dichotomous

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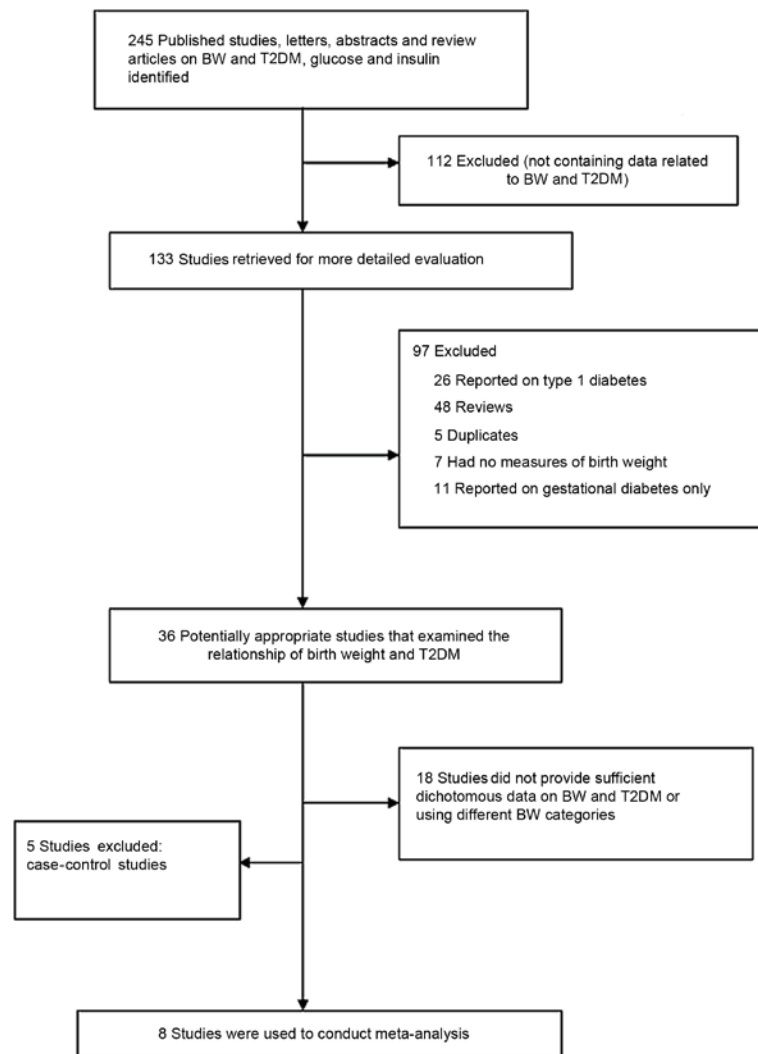
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Figure 1. Summary of the article selection process. BW, birth weight; T2DM, type 2 diabetes mellitus.
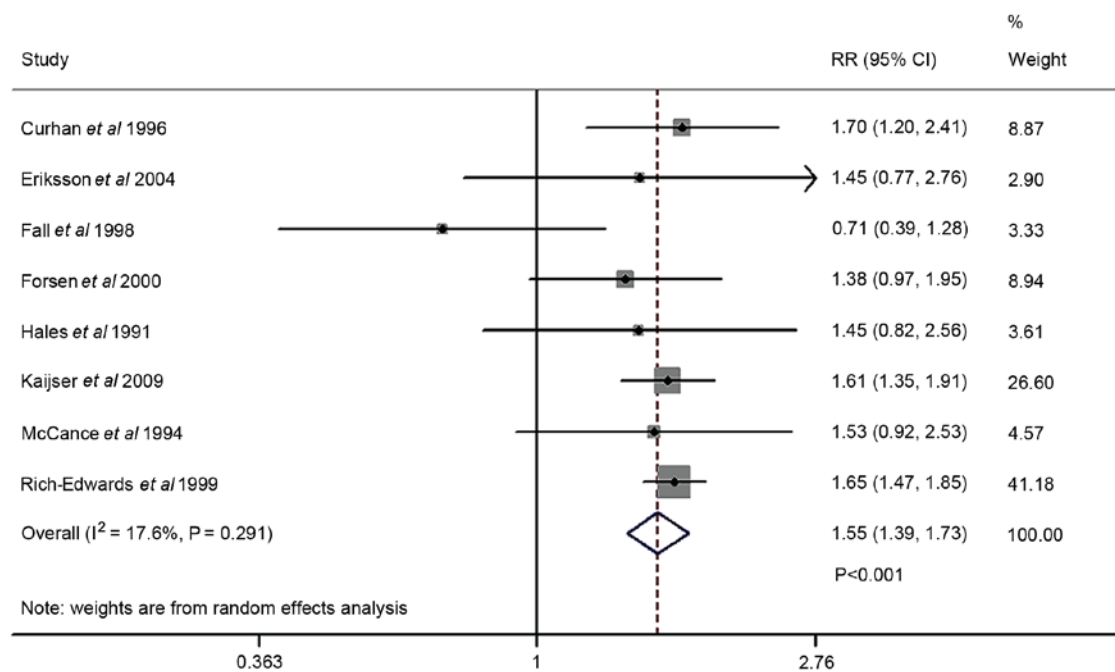

Figure 2. Forest plot comparing type 2 diabetes risk in low birth weight (<2,500 g) and normal birth weight subjects (2,500-4,000 g). The RR were calculated using a random-effects model. 95% CIs are indicated in parentheses and as horizontal bars. CI, confidence interval; RR, relative risk.

data on T2DM and low birth weight; and iii) presented relative risk (RR) and 95% confidence intervals (CI), or data with which to calculate them, for T2DM in at least two strata of birth weight. Birth weight was required to be expressed in a specific range, such as <2,500 and >2,500 g, or <4,000 and >4,000 g. Alternatively, an RR and 95% CI for the change in T2DM risk per unit change in birth weight could have been reported. Studies were considered irrespective of the definition of T2DM (definitions used included those of the World Health Organization (24), the National Diabetes Data Group (25) and the America Diabetes Association (26).

Data extraction. A standard extraction form was used to collect the following information from each study: First author name, year of publication, country in which the study was conducted, year of patient birth, patient age, trend declared by the study's authors, final cohort size and number of cases with T2DM. Data were extracted independently by two investigators. Discrepancies, if any, were resolved by discussion and consultation with a third reviewer.

Quality assessment. Two investigators performed a quality assessment using the Newcastle-Ottawa scale (27) for included studies. This scale allocates a maximum of nine stars for the highest quality of selection, comparability and ascertainment of exposure to risks. The four criteria in evaluating the selection were as follows: i) Representativeness of the low birth weight; ii) selection of the non-low birth weight; iii) ascertainment of low birth weight; and iv) demonstration that T2DM was not present at the start of the study. A maximum of two stars was awarded for comparability: i) Study controls for age; and ii) study controls for any additional factors. The three criteria in evaluating the outcomes were as follows: i) Assessment of T2DM; ii) follow-up was long enough for T2DM to occur (>10 years); and iii) adequacy of follow-up of cohort (>80%). The two authors discussed the implementation of this assessment tool and agreed on a method of implementation prior to their independent assessment of studies.

Statistical analysis. Meta-analysis was conducted using Review Manager (version 5.1; The Nordic Cochrane Centre, Copenhagen, Denmark). Measurement data were presented as the weighted mean difference and 95% CI. Enumerated data were presented as the odds ratio (OR) and 95% CI. Cochran's Q statistic and I^2 statistic were used to assess heterogeneity. If significant heterogeneity was observed, the random-effects model was used. Otherwise, the fixed-effects model was used (28,29). P<0.05 was considered to indicate a statistically significant result.

Publication bias was assessed by inspection of a funnel plot and formal testing for funnel plot asymmetry was performed using Begg's test and Egger's test. Sensitivity analysis was performed by excluding one study at a time to identify the influence of individual data sets on the pooled RR.

Results

Preliminary screening of literature. A total of 245 studies related to birth weight and T2DM were identified during the literature

Table I. Characteristics of eight studies included in the meta-analysis.

First author, year	Country	Year of birth	Age, years	Trend declared by the study's authors	Birth weight reference category for adjusted estimate, g	Final cohort size, n	Cases with type 2 diabetes, n	(Refs.)
Curhan et al, 1996	USA	1911-1946	40-75	Linear inverse	3,180-3,810	22,846	424	(34)
McCance et al, 1994	USA	1940-1972	20-39	U-shaped	2,500-4,499	1,179	210	(21)
Rich-Edwards et al, 1999	USA	1921-1946	60	Linear inverse	3,260-3,820	69,526	2,123	(35)
Hales et al, 1991	England	1920-1930	59-70	Linear inverse	-	370	27	(36)
Fall et al, 1998	India	1934-1953	39-60	Linear positive	-	501	75	(37)
Forsén et al, 2000	Finland	1924-1933	64-73	Linear inverse	-	7,044	471	(38)
Eriksson et al, 2004	Sweden	1913-1963	50	Linear inverse	3,000-4,250	478	54	(39)
Kaijser et al, 2009	Sweden	1925-1949	37-62	Linear inverse	1,500-4,000	6,425	508	(40)

Table II. Assessment of study quality based on the Newcastle-Ottawa scale.

First author, year	Selection (stars out of 4)	Comparability (stars out of 2)	Exposure (stars out of 3)	(Refs.)
Curhan *et al*, 1996	★★★	★	★★	(34)
McCance *et al*, 1994	★★★	★★	★★	(21)
Rich-Edwards *et al*, 1999	★★	★★	★★	(35)
Hales *et al*, 1991	★★★	★	★★	(36)
Fall *et al*, 1998	★★★	★	★★	(37)
Forsen *et al*, 2000	★★★	★	★★	(38)
Eriksson *et al*, 2004	★★★★	★★	★★★	(39)
Kaijser *et al*, 2009	★★★	★	★★	(40)

Table III. Result of leave-one-out sensitivity analysis; low birth weight vs. normal birth weight).

First author, year	I^2 (%)	P-value	(Refs.)
Curhan *et al*, 1996	28.0	0.215	(34)
McCance *et al*, 1994	29.2	0.206	(21)
Rich-Edwards *et al*, 1999	19.8	0.278	(35)
Hales *et al*, 1991	28.5	0.211	(36)
Fall *et al*, 1998	0.0	0.973	(37)
Forsen *et al*, 2000	23.5	0.250	(38)
Eriksson *et al*, 2004	28.7	0.209	(39)
Kaijser *et al*, 2009	29.0	0.207	(40)

Table V. Result of leave-one-out sensitivity analysis; low birth weight vs. high birth weight.

First author, year	I^2 (%)	P-value	(Refs.)
Curhan *et al*, 1996	43.4	0.116	(34)
Eriksson *et al*, 2004	42.7	0.121	(39)
Forsen *et al*, 2000	45.3	0.104	(38)
Hales *et al*, 1991	22.5	0.265	(36)
Kaijser *et al*, 2009	35.4	0.171	(40)
McCance *et al*, 1994	24.2	0.253	(21)
Rich-Edwards *et al*, 1999	34.7	0.176	(35)

Table IV. Result of leave-one-out sensitivity analysis; birth weight vs. normal birth weight).

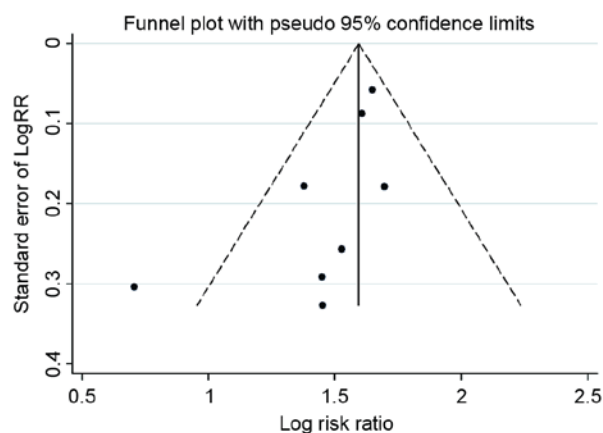| First author, year	I^2 (%)	P-value	(Refs.)
Curhan *et al*, 1996	71.6	0.003	(34)
McCance *et al*, 1994	64.5	0.015	(21)
Rich-Edwards *et al*, 1999	63.0	0.019	(35)
Hales *et al*, 1991	56.3	0.043	(36)
Forsen *et al*, 2000	67.4	0.009	(38)
Eriksson *et al*, 2004	72.0	0.003	(39)
Kaijser *et al*, 2009	70.2	0.005	(40)

Figure 3. Funnel plot of studies evaluating the association between birth weight (low, <2,500 g vs. normal, 2,500-4,000 g) and diabetes. RR, relative risk.

search. However, 237 studies were excluded for the following reasons: i) Did not contain birth weight and T2DM data (n=112); ii) reported on type 1 diabetes (n=26); iii) review articles (n=48); iv) duplicates (n=5); v) did not contain birth weight-related data (n=7); vi) reported on gestational diabetes (n=11); vii) did not present binary data about birth weight and T2DM and did not use the indicated birth weight range (n=18); viii) case-control studies (n=5) (23,30-33). The remaining eight studies were selected in order to conduct the meta-analysis (Fig. 1) (21,34-40).

The eight included studies are presented in Table I. A total of 108,369 individuals were included in these studies and 3,892 were diagnosed with T2DM. All eight studies indicated the OR value of T2DM through comparing low birth weight (<2,500 g) and normal birth weight (2,500-4,000 g). Seven studies indicated the OR value of T2DM through comparing normal birth weight and high birth weight (>4,000 g). These seven studies also indicated the OR value through comparing
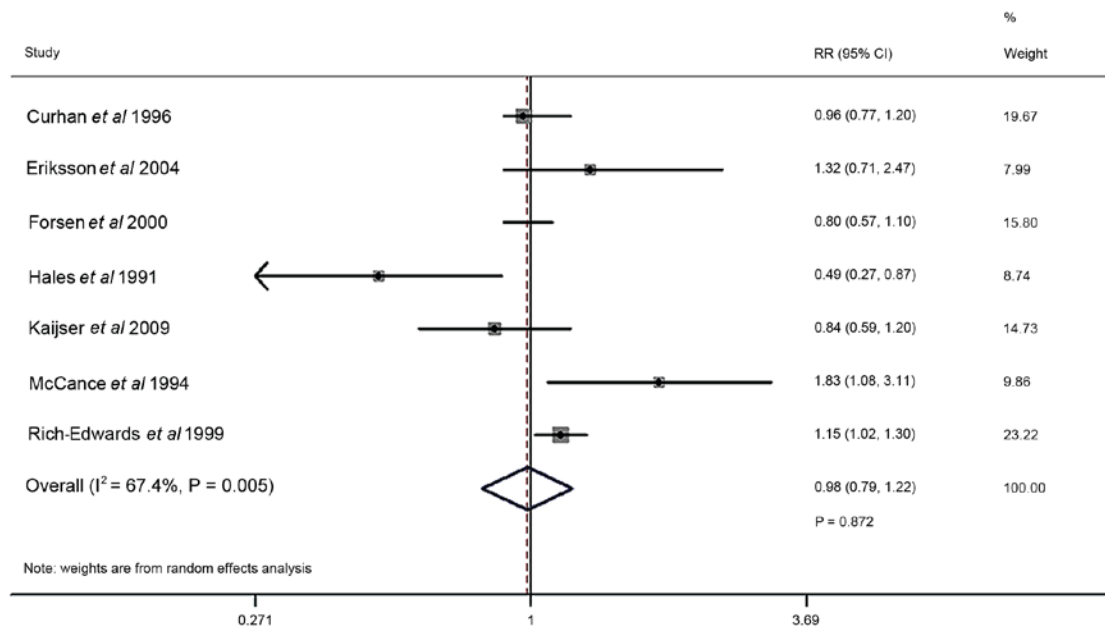
Figure 4. Forest plot comparing type 2 diabetes risk in high birth weight (>4,000 g) and normal birth weight subjects (2,500-4,000 g). The RR were calculated using a random-effects model. 95% CIs are indicated in parentheses and as horizontal bars. CI, confidence interval; RR, relative risk.

low birth weight and high birth weight. In one study, there was a U-shaped curve relationship between birth weight and T2DM. Furthermore, one study reported that birth weight was positively associated with T2DM. There was a linear inverse trend in 6 studies. According to the Newcastle-Ottawa scale, the mean score for the selection, comparability and exposure for the included studies was 6.5 stars (Table II).

Meta-analysis results. The forest plot comparing T2DM risk in cases of low birth weight and normal birth weight is presented in Fig. 2. The T2DM risk analysis was included in eight studies. Random-effects model assessment ($Q^2=8.49$; P=0.291; $I^2=17.6\%$) indicated that low birth weight increased the risk of T2DM compared with normal birth weight (OR=1.55; 95% CI, 1.39-1.73; P<0.001). Sensitivity analysis indicated that the pooled ORs were no statistically significant no matter what study was excluded from analysis, suggesting the robustness of results. This analysis also revealed that one study, by Fall *et al* (37), was the largest source of heterogeneity (Table III). The I^2 measure for low birth weight markedly declined from 17.6 to 0.0% when this study was omitted. Homogeneity was achieved after excluding Fall *et al* (37) [Q=1.28; degrees of freedom (df)=6; P=0.973; $I^2=0.00$) and an RR of 1.62 was obtained (95%CI, 1.478-1.754; fixed-effects; P<0.001; data not shown). A funnel plot (Fig. 3) and Begg's and Egger's tests were conducted to assess the publication bias of the included studies. Evidence of publication bias was also not seen with the Egger's or Begg's tests (Egger's, P=0.103; Begg's, P=0.083; data not shown).

The forest plot of T2DM risk comparing high birth weight and normal birth weight is presented in Fig. 4. The risk analysis was conducted in 7 studies. Random-effects model assessment ($Q^2=18.38$; P=0.005; $I^2=67.4\%$) indicated that there was no significant association between high birth weight and T2DM (OR=0.98; 95% CI, 0.79-1.22; P=0.872). Sensitivity analysis revealed that one study by Hales *et al* (36) was the
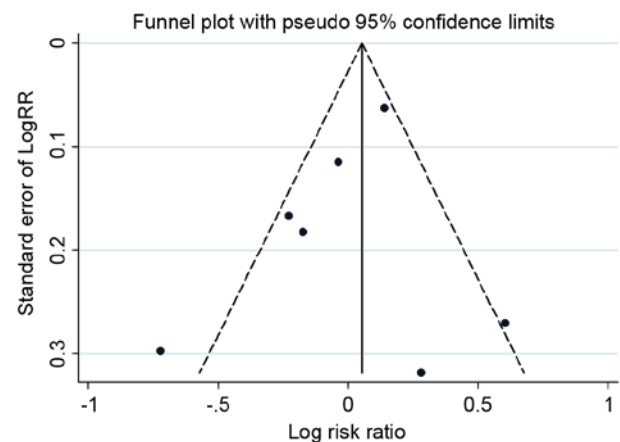

Figure 5. Funnel plot of studies evaluating the association between birth weight (high, >4,000 g vs. normal, 2,500-4,000 g) and diabetes. RR, relative risk.

largest source of heterogeneity (Table IV). The I^2 measure for high birth weight markedly declined from 67.4 to 56.3% when this study was omitted. A funnel plot (Fig. 5) and Begg's and Egger's tests were conducted to assess the publication bias of the included studies. No evidence of publication bias was observed. Evidence of publication bias was also not observed with the Egger's or Begg's tests (Egger's, P=0.167; Begg's, P=0.024; data not shown).

The forest plot comparing T2DM risk in cases of low birth weight and high birth weight is presented in Fig. 6. The risk analysis was conducted in 7 studies. Random-effects model assessment ($Q^2=9.45$; P=0.150; $I^2=36.5\%$) indicated that low birth rate was associated with a higher risk of T2DM compared with high birth weight (RR, 1.58; 95% CI 1.30-1.93; P<0.001). Sensitivity analysis revealed that one study, by McCance *et al* (21), was the largest source of heterogeneity (Table V). The I^2 measure for low birth weight markedly
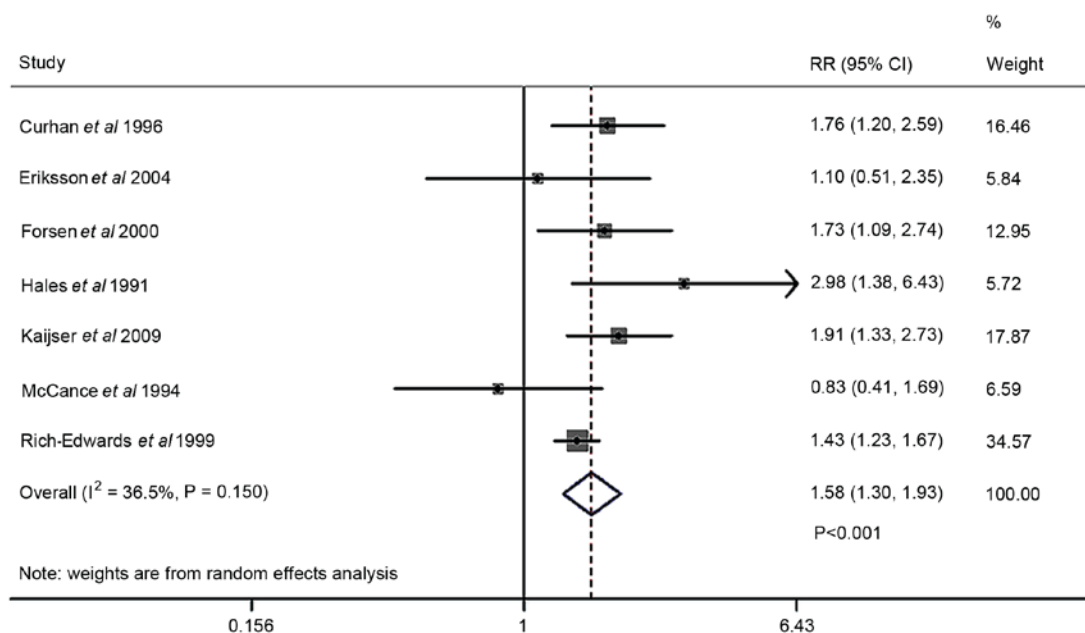
Figure 6. Forest plot comparing type 2 diabetes risk in low birth weight (<2,500 g) and high birth weight subjects (>4,000 g). The RR were calculated using a random-effects model. 95% CIs are indicated in parentheses and as horizontal bars. CI, confidence interval; RR, relative risk.

declined from 36.5 to 24.2%. Homogeneity was achieved after excluding a study (Q=6.59; df=5; P=0.253; I^2=24.2%), and an OR of 1.63 was obtained (95% CI, 1.367-1.937; fixed-effects; P<0.001). A funnel plot (Fig. 7) and Begg's and Egger's tests were conducted to assess the publication bias of the included studies. Evidence of publication bias was also not observed with the Egger's or Begg's tests (Egger's, P=0.663; Begg's. P=0.881; data not shown).

Discussion

Previous studies have demonstrated that birth weight is associated with chronic diseases, including obesity (41), cardiovascular disease (42) and hypertension (43). However, the association between birth weight and T2DM is still unclear. Some studies have demonstrated a U-shaped curve relationship between them (20-22), while other studies have indicated a negative linear association (18,44-46). In the present study, a meta-analysis of the published literature was conducted, which studied the association between birth weight and T2DM. A total of eight studies were selected for analysis. Forest plots were constructed comparing T2DM risk in cases of low and normal birth weight, high and normal birth weight, and low and high birth weight, respectively. The analysis indicated that low birth weight increased the risk of T2DM and high birth weight had no notable influence on the risk of T2DM.

The studies indicated that low birth weight was related to T2DM; however, the mechanism by which low birth weight increases the risk of T2DM remains unclear (47-52). Some research has suggested that it may be a compensatory adaptation to an adverse intrauterine environment during fetal development. The smaller fetus and structural and functional change of important organs leads to insulin resistance and abnormal islet development, which could cause diabetes in adults (53). A lack of nutrients may have a permanent influence
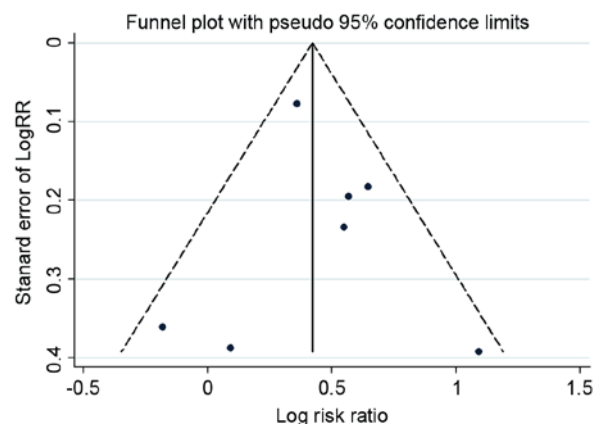

Figure 7. Funnel plot of studies evaluating the association between birth weight (low, <2,500 g vs. high, >4,000 g) and diabetes. RR, relative risk.

on the fetal metabolism, increasing the risk of obesity and T2DM in adults (54).

Some studies employed ^{31}P magnetic resonance spectroscopy and identified that glycolysis was decreased in cases of low birth weight. The adipose tissue in muscles also was decreased in these cases (55,56). Indirect calorimetry or carbohydrate metabolism efficiency using ^{13}C indicated that the oxidation ability of postprandial glucose was decreased in cases of low birth weight (57). These studies are instrumental to understanding a possible mechanism between low birth weight and T2DM.

Poor intrauterine nutrition leads to low birth weight (58). For a fetus with low birth weight, leptin level was increased during childhood and adiponectin level was also positively related to birth weight, which increased the incidence rate of T2DM (59). This suggests that low birth weight may be a clinical marker of poor intrauterine environment and a potential risk factor for T2DM.

The present study has several limitations that require further consideration. Due to limited data, it was not possible to perform further stratification analyses of other potential influencing factors, including gender.

In conclusion, the current meta-analysis demonstrated that low birth weight increases the risk of T2DM. Low birth weight may be a potential risk factor and marker for T2DM. Further research is required to elucidate the etiopathogenic mechanisms behind this association.

Acknowledgements

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