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Meta-Analysis

Birth Weight and Subsequent Risk of Type 2 Diabetes: A Meta-Analysis

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The "small baby syndrome hypothesis" suggests that an inverse linear relation exists between birth weight and risk of type 2 diabetes. The authors conducted a meta-analysis to examine this association. They included studies that reported odds ratios and 95% confidence intervals (or data with which to calculate them) for the association of type 2 diabetes with birth weight. Fourteen studies involving a total of 132,180 persons were identified. Low birth weight (<2,500 g), as compared with a birth weight of ≥2,500 g, was associated with increased risk of type 2 diabetes (odds ratio (OR) = 1.32, 95% confidence interval (CI): 1.06, 1.64). High birth weight (>4,000 g), as compared with a birth weight of ≤4,000 g, was associated with increased risk to the same extent (OR = 1.27, 95% CI: 1.01, 1.59). Pooled estimates increased further when normal birth weight (2,500–4,000 g) was used as the reference category (low birth weight: OR = 1.47, 95% CI: 1.26, 1.72; high birth weight: OR = 1.36, 95% CI: 1.07, 1.73). Meta-regression and categorical analyses showed a U-shaped relation between birth weight and diabetes risk. These findings indicate that there exists a relation between birth weight and later-life risk of type 2 diabetes which is not linearly inverse but U-shaped.

birth weight; diabetes mellitus, type 2; meta-analysis

Abbreviations: CI, confidence interval; OR, odds ratio.

In 1993, Barker et al. (1) published highly influential findings indicating a relation between low birth weight and increased risk of developing symptoms of the metabolic syndrome. Subsequently, a number of studies found an association between low birth weight and risk of type 2 diabetes mellitus (2–4). Many authors claimed that the relation between birth weight and type 2 diabetes is inversely linear, implying that high birth weight leads to decreased risk (5, 6). However, some researchers have found that high birth weight but not low birth weight is followed by increased risk of type 2 diabetes (7) or have found an increased risk in both low birth weight and high birth weight subjects (8, 9).

Since the prevalences of both high birth weight and low birth weight are increasing (10), this issue might have high relevance for public health. Therefore, we performed a meta-analysis of the relation between birth weight and subsequent risk of type 2 diabetes.

MATERIALS AND METHODS

Study base

We systematically searched the literature according to the MOOSE guidelines for meta-analyses of observational studies (11), including the databases MEDLINE (1966–2005) and EMBASE (1989–2005). We used the terms "birth weight," "type 2 diabetes," "non-insulin-dependent diabetes mellitus," and "NIDDM" in the full-text option, without language restrictions. Furthermore, we manually searched all references cited in original studies and reviews identified.

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TABLE 1. Characteristics of 14 studies included in a meta-analysis of birth weight and risk of type 2 diabetes mellitus, 1966–2005

Reference	Country	Study design	Year of birth	Age (years)	% lost to follow-up	Final cohort size	No. of cases with type 2 diabetes
Barker et al., 2002 (15)	Finland	Cohort	1924–1944	53–73	15	13,517	698
Carlsson et al., 1999 (16)	Sweden	Cohort	1938–1957	35–56	83	2,294	35
Curhan et al., 1996 (2)	United States	Cohort	1911–1946	40–75	56	22,846	424
Dyck et al., 2001 (7 (I))	Canada	Case-control	1950–1984	10–45	27	1,728	846
Dyck et al., 2001 (7 (II))	Canada	Case-control	1950–1984	10–45	27	2,264	1,164
Eriksson et al., 2003 (17)	Finland	Cohort	1934–1944	40	17	8,702	292
Fall et al., 1998 (18)	India	Cohort	1934–1953	39–60	7	501	75
Forsén et al., 2000 (19)	Finland	Cohort	1924–1933	64–73	0.6	7,044	471
Hales et al., 1991 (20)	United Kingdom	Cohort	1920–1930	59–70	68	370	27
Lithell et al., 1996 (3)	Sweden	Cohort	1920–1924	60	61	1,093	61
McCance et al., 1994 (8)	United States	Cohort	1940–1972	20–39	53	1,179	210
Rich-Edwards et al., 1999 (4)	United States	Cohort	1921–1946	60	43	69,526	2,123
Wei et al., 2003 (9)	Taiwan	Case-control	1992–1997	6–18	74	978	429
Young et al., 2002 (21)	Canada	Case-control	Not reported	<18	Not reported	138	46

To be eligible, a study had to fulfill the following criteria: 1) it had to be an original report on the relation between birth weight and type 2 diabetes; and 2) odds ratios and 95 percent confidence intervals (or data with which to calculate them) for type 2 diabetes in at least two strata of birth weight had to have been presented. Alternatively, an odds ratio and 95 percent confidence interval for the change in type 2 diabetes risk per unit change in birth weight had to have been reported. Studies were considered irrespective of the definition of type 2 diabetes (definitions used included those of the World Health Organization (12), the National Diabetes Data Group (13), and the American Diabetes Association (14)). Thirteen articles on original studies were identified (2–4, 7–9, 15–21). One article described two studies (7), so 14 original studies (10 cohort studies and four case-control studies) were included. From these reports, data were abstracted in duplicate, using a standardized form.

Statistical analysis

Five different meta-analytic approaches were used: 1) A birth weight cutoff of 2,500 g (low birth weight) (22) was used to compare the risks of type 2 diabetes below and above this value (dichotomous comparison). 2) The dichotomous approach was repeated for a birth weight cutoff of 4,000 g (high birth weight) (22). 3) Both dichotomous comparisons were repeated, but normal birth weight (2,500–4,000 g) was used as the reference category. 4) A weighted meta-regression analysis was performed. 5) Pooled odds ratios for type 2 diabetes were calculated separately for seven predefined categories of birth weight, using 500-g intervals.

Dichotomous comparisons. We extracted data on numbers of subjects with and without type 2 diabetes above or below the cutoff value and calculated corresponding crude odds ratios and 95 percent confidence intervals. We constructed both fixed-effects and random-effects models to estimate the pooled odds ratios for risk of type 2 diabetes above versus below the respective cutoff values across all studies. A Cochrane Q-based test was used to assess heterogeneity.

Meta-regression analysis. For meta-regression, the birth-weight-specific odds ratio had to be related to the respective birth weight. Since birth weights were reported as categorical data with a certain range in the studies (e.g., 2,000–2,500 g, 3,000–3,500 g, etc.), the median of the upper and lower limits of each category was assigned to the particular estimate in each study (23). Estimates were plotted against birth weight. Since visual inspection of the scatterplot revealed a U-shaped relation, we performed a weighted meta-regression analysis with birth weight and (birth weight $\times$ birth weight) used as covariates (random-effects model).

Categorical analysis. Pooled odds ratios for type 2 diabetes were calculated in seven predefined categories of birth weight, each covering a 500-g interval: $\leq$2,000 g, 2,001–2,500 g, 2,501–3,000 g, 3,001–3,500 g, 3,501–4,000 g, 4,001–4,500 g, and >4,500 g. For calculation of category-specific odds ratios, in each study the lowest category of birth weight was defined as the reference category. If more than one estimate from one individual study was located within the same predefined category of birth weight, as defined above, we used the pool-first approach (23) to obtain a single study-specific odds ratio for each category of birth weight. Since the Cochrane Q-based test revealed significant heterogeneity in each case, a random-effects model was used throughout.

Influence analysis. The robustness of the pooled estimate was checked by influence analysis (random-effects model). Each study estimate was individually omitted from the data set, followed in each case by recalculation of the pooled estimate of the remaining studies.

TABLE 2. Characteristics of 14 studies included in a meta-analysis of birth weight and risk of type 2 diabetes mellitus, 1966–2005

Reference	Assessment of birth weight	Assessment of type 2 diabetes	Trend declared by the study's authors	Confounding factors considered	Birth weight reference category (g) for adjusted estimate	Remarks
Barker et al., 2002 (15)	Records	Register of medication	Linear inverse	Year of birth, sex	Not applicable*	
Carlsson et al., 1999 (16)	Questionnaires	Clinical examinations	Linear inverse	Age, BMI†, family history of diabetes	3,001–3,600	Men only
Curhan et al., 1996 (2)	Questionnaires	Questionnaires	Linear inverse	Age, BMI, parental history of diabetes	3,180–3,810	Men only
Dyck et al., 2001 (7 (I))	Records	Register	Linear positive	Age, sex, maternal age, parity, previous stillbirth, gestational age	2,500–4,000	
Dyck et al., 2001 (7 (II))	Records	Register	Linear positive	Age, sex, maternal age, parity, previous stillbirth	2,500–4,000	
Eriksson et al., 2003 (17)	Records	Register of medication	Linear inverse	Not reported		
Fall et al., 1998 (18)	Records	Clinical examinations	Linear positive	Not reported		
Forsén et al., 2000 (19)	Records	Register	Linear inverse	Weight at age 7 years	Not applicable*	
Hales et al., 1991 (20)	Records	Clinical examinations	Linear inverse	Not reported		Incident cases only
Lithell et al., 1996 (3)	Records	Clinical examinations	Linear inverse	BMI at age 50 years	>3,250	Men only
McCance et al., 1994 (8)	Records	Clinical examinations	U-shaped	Age, BMI, maternal diabetes	2,500–4,499	Men only
Rich-Edwards et al., 1999 (4)	Questionnaires	Records	Linear inverse‡	Age, adult BMI, maternal history of diabetes, gestational age	3,260–3,820	Women only
Wei et al., 2003 (9)	Register	Clinical examinations	U-shaped	Age, sex, BMI, family history of diabetes, socioeconomic status, gestational diabetes	3,000–3,499	
Young et al., 2002 (21)	Interview	Records	U-shaped	Diabetes during pregnancy, diet, smoking during pregnancy, alcohol drinking during pregnancy, mother's prepregnancy BMI, breastfeeding	2,500–4,000	

* Only the adjusted odds ratio for a 1,000-g increase in birth weight was reported.
† BMI, body mass index.
‡ See text.

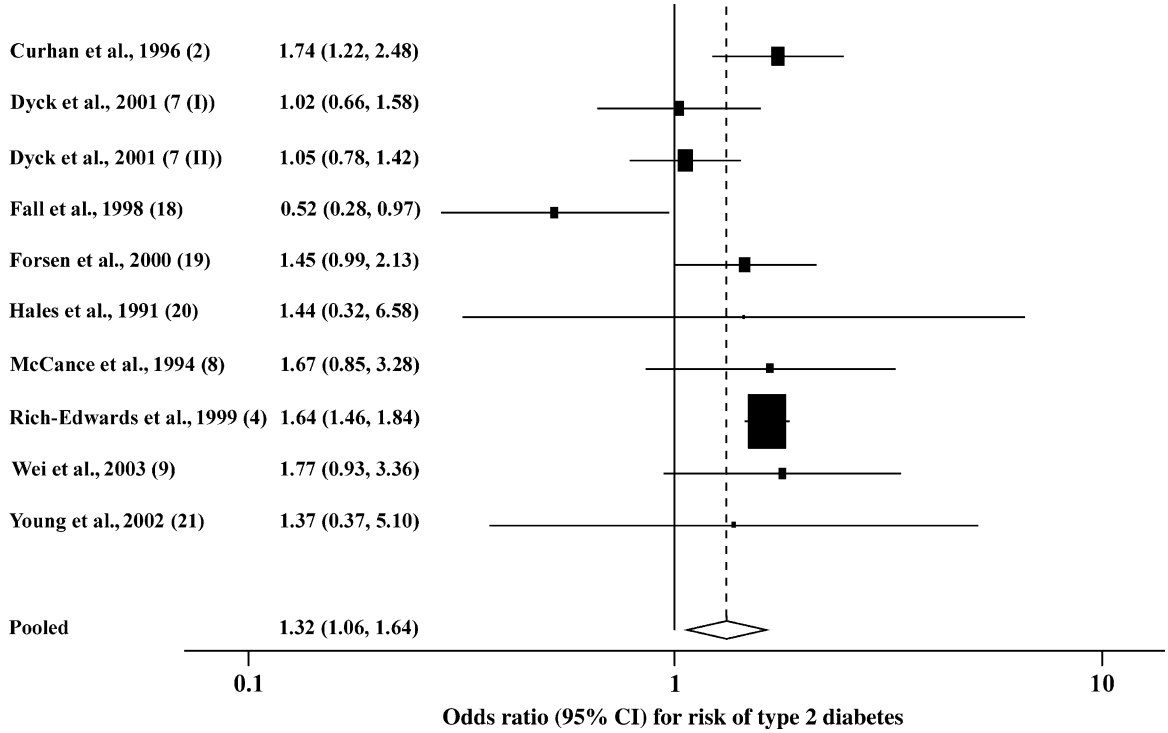

FIGURE 1. Odds ratios for type 2 diabetes mellitus in subjects with birth weights <2,500 g as compared with subjects with birth weights ≥2,500 g in a meta-analysis (1966–2005). Studies are ordered alphabetically by first author. The pooled odds ratio (diamond) was calculated by means of a random-effects model. 95% confidence intervals (CIs) are shown in parentheses and as horizontal bars.

Publication bias and statistical software. Publication bias was assessed by inspection of the funnel plot and formal testing for funnel plot asymmetry using Begg's test and Egger's test. All calculations were carried out using Stata, version 8 (Stata Corporation, College Station, Texas).

RESULTS

Study characteristics are displayed in tables 1 and 2. The studies involved a total of 132,180 persons, of whom 6,901 had type 2 diabetes. Ten studies (2, 4, 7 (I), 7 (II), 8, 9, 18–21) provided data for calculation of odds ratios for type 2 diabetes in subjects with low birth weight (<2,500 g), as compared with subjects above this cutoff value. From nine studies (2, 4, 7 (I), 7 (II), 8, 9, 17, 19, 21), data for calculation of odds ratios for type 2 diabetes in probands with high birth weight (>4,000 g) could be extracted. In eight studies (2, 4, 7 (I), 7 (II), 8, 9, 19, 21), results for both low birth weight and high birth weight were reported. In three studies (3, 15, 16), only odds ratios per 1,000-g linear increase in birth weight were reported.

In seven studies (2, 3, 15–17, 19, 20), a linear inverse relation between birth weight and type 2 diabetes risk was reported, while in three studies (7 (I), 7 (II), 18) a linear positive association was found. In three studies (8, 9, 21), a U-shaped relation was declared. Remarkably, in one further study (4), a linear inverse relation was indicated in the abstract, while data presented in the main text showed a U-shaped relation. In that case, we decided to use the data reported in the main text.

Figure 1 shows the forest plot for risk of type 2 diabetes in subjects with low birth weight as compared with subjects with birth weights ≥2,500 g. Low birth weight was associated with increased risk of type 2 diabetes in the random-effects model as well as the fixed-effects model (odds ratio (OR) = 1.49, 95 percent confidence interval (CI): 1.36, 1.64). The results of the studies were significantly heterogeneous ($p = 0.007$). The study by Rich-Edwards et al. (4) largely influenced the pooled odds ratio: Omitting this study from the data set led to a pooled estimate that was closer to 1.0 and was not significant (OR = 1.25, 95 percent CI: 0.97, 1.59).

High birth weight was associated with increased risk of type 2 diabetes to the same extent as low birth weight (figure 2). This effect was also observed in the fixed-effects model (OR = 1.26, 95 percent CI: 1.12, 1.42). Again, significant heterogeneity of study results was found ($p = 0.001$). Contrary to the above-mentioned finding on the relation between low birth weight and risk of type 2 diabetes, influence analysis did not reveal a particular impact of one of the studies on the pooled odds ratio (data not shown).

Given these findings of increased risk of type 2 diabetes at both ends of the birth weight spectrum, we repeated the dichotomous comparisons, now using ''normal birth weight'' (2,500–4,000 g) as the reference category for all studies that gave data on both low and high birth weight. As expected, the pooled estimates for both low birth weight and high birth

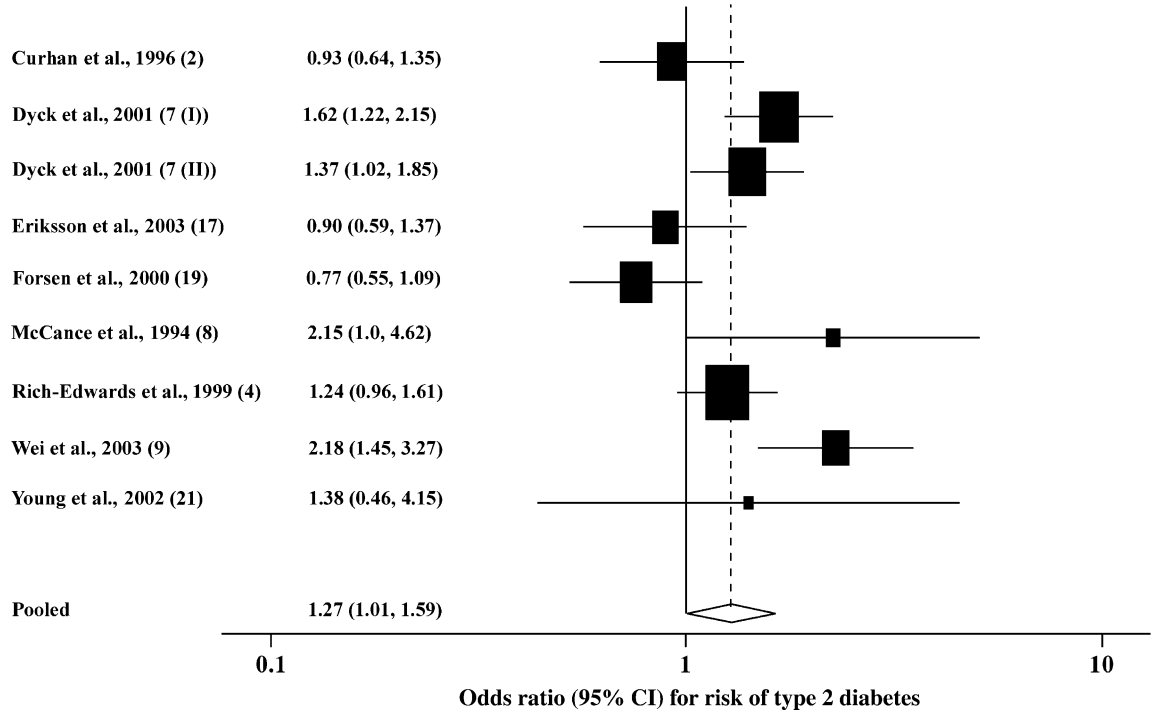

FIGURE 2. Odds ratios for type 2 diabetes mellitus in subjects with birth weights >4,000 g as compared with subjects with birth weights ≤4,000 g in a meta-analysis (1966–2005). Studies are ordered alphabetically by first author. The pooled odds ratio (diamond) was calculated by means of a random-effects model. 95% confidence intervals (CIs) are shown in parentheses and as horizontal bars.

weight increased (figure 3). The fixed-effects model produced similar results (low birth weight: OR = 1.55, 95 percent CI: 1.41, 1.70; high birth weight: OR = 1.34, 95 percent CI: 1.18, 1.52).

From all 14 studies, 54 estimates for specific categories of birth weight could be extracted for meta-regression. Scatterplots revealed that the relation between birth weight and type 2 diabetes risk was U-shaped. In weighted meta-regression analysis, both birth weight and (birth weight × birth weight) were significantly related to risk of type 2 diabetes (regression coefficients: for birth weight, −0.0011, 95 percent CI: −0.0018, −0.004 ($p = 0.003$); for birth weight × birth weight, 1.50×10^{-7}, 95 percent CI: 4.43×10^{-8}, 2.55×10^{-7} ($p = 0.005$)) (figure 4).

Table 3 shows the results of the categorical analysis. Compared with the lowest birth weight category (≤2,000 g), risk of type 2 diabetes initially decreased by increasing birth weight within the normal range, to an odds ratio of 0.55 (95 percent CI: 0.48, 0.62) in the category 3,501–4,000 g. Thereafter, risk of type 2 diabetes increased with increasing birth weight, resembling the U-shaped relation found by means of meta-regression analysis.

Neither for the relation between low birth weight and type 2 diabetes nor for that between high birth weight and type 2 diabetes was evidence of publication bias found, as indicated by visual inspection of funnel plots (not shown) and nonsignificant Begg's tests (low birth weight: $p = 0.72$; high birth weight: $p = 0.92$) and Egger's tests (low birth weight: $p = 0.20$; high birth weight: $p = 0.84$).

DISCUSSION

During recent years, it has often been postulated that an inverse linear relation exists between birth weight and risk of type 2 diabetes (1, 3, 5, 6), leading to the conclusion that a higher birth weight may even result in decreased mortality from type 2 diabetes (24). Applying different meta-analytic techniques, however, we found that the relation between birth weight and type 2 diabetes is not linearly inverse but U-shaped.

Although more original reports were published which investigated this issue, our systematic review revealed that to date, only 10 published studies have adhered to basal standards of study quality by providing essential data with which to perform quantitative data synthesis on the internationally intensively discussed relation between low birth weight (<2,500 g) and risk of type 2 diabetes. Considering the intensive discussion of the "fetal origins hypothesis," one might be surprised that no more original studies were eligible. However, according to basal requirements for quantitative data synthesis, a number of studies did not provide sufficient information with which to calculate an odds ratio. Among them were some of the most often cited studies on the relation between low birth weight and type 2 diabetes (1). Furthermore, a number of well-known studies only analyzed surrogate measures like insulin resistance as outcome parameters, instead of type 2 diabetes.

The relatively low number of studies providing sufficient data on the relation between low birth weight and type 2

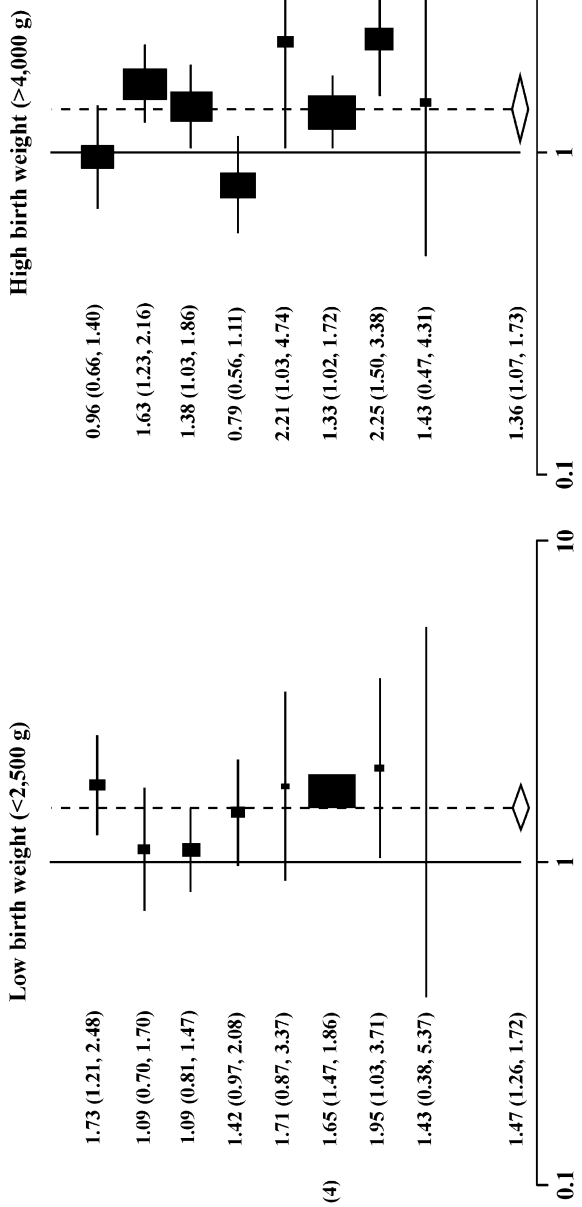

FIGURE 3. Odds ratios for type 2 diabetes mellitus in subjects with low birth weights (<2,500 g) (left) and high birth weights (>4,000 g) (right), as compared with subjects with birth weights of 2,500–4,000 g, in a meta-analysis (1966–2005). The pooled odds ratios (diamonds) were calculated by means of a random-effects model. 95% confidence intervals (CIs) are shown in parentheses and as horizontal bars.

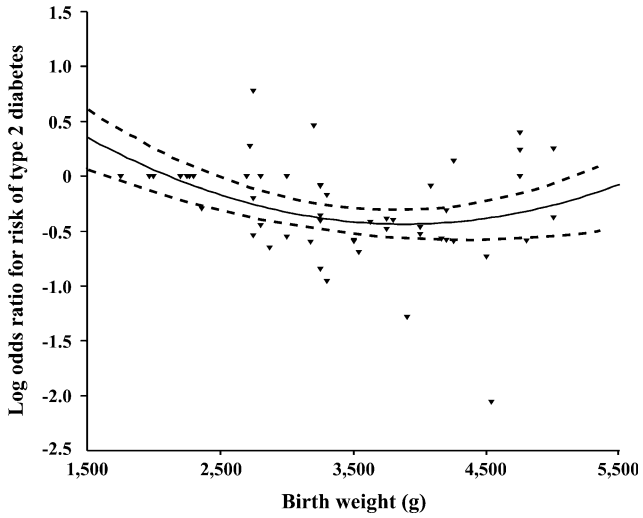

FIGURE 4. Scatterplot and meta-regression curve (mean and corresponding 95% confidence interval) of log odds ratios for type 2 diabetes mellitus by birth weight in a meta-analysis (1966–2005). A total of 14 studies provided 54 estimates of the relation between birth weight and risk of type 2 diabetes. Weighted meta-regression revealed a significant U-shaped relation between birth weight and diabetes risk (for details, see text).

diabetes conflicts with the 47 narrative reviews (MEDLINE, 1966–2005) which have purported to summarize the available knowledge on this topic (search history and bibliographic data are available from the authors upon request). Remarkably, 46 of these reviews concluded that an inverse linear relation exists between birth weight and type 2 diabetes. By contrast, our meta-analysis indicated that high birth weight is a risk factor for type 2 diabetes to the same extent as low birth weight.

However, only in a small proportion of the 14 studies analyzed here did the authors of the papers themselves report a U-shaped association. Several explanations can be provided for this discrepancy with the results of our meta-analytic approach. Some studies were performed in populations which did not include persons with high birth weight (18). In a number of studies, only linear trends between birth weight and risk of type 2 diabetes were analyzed (3, 15, 16). In other studies, investigators performed statistical adjustments on potential nonconfounders or causal intermediates, which selectively weakened the association between high birth weight and type 2 diabetes risk but not that between low birth weight and diabetes risk. Thereby, our results underscore one of the advantages of meta-analysis: The study estimates summarized came not only from studies that described positive linear or U-shaped relations but also from studies that did not primarily investigate the effect of high birth weight but did provide data for its calculation. Consequently, when a ''normal'' range of birth weight (2,500–4,000 g) was used as the reference category, the pooled odds ratios for risk of type 2 diabetes were increased for both low birth weight and high birth weight. This further highlights the importance of the definition of the reference group, based on an uncommitted working hypothesis, for interpreting results from studies of the impact of birth weight on later risk of disease.

TABLE 3. Odds ratio for type 2 diabetes mellitus by birth weight in a meta-analysis, 1966–2005*

Birth weight (g)	No. of estimates†	Odds ratio	95% confidence interval
≤2,000	5	1.00	0.84, 1.19
2,001–2,500	6	0.82	0.69, 0.98
2,501–3,000	10	0.82	0.61, 1.08
3,001–3,500	11	0.72	0.59, 0.89
3,501–4,000	8	0.55	0.48, 0.62
4,001–4,500	7	0.60	0.51, 0.70
>4,500	7	0.92	0.63, 1.34

* Categorical analysis (random-effects model). The lowest category of birth weight was used as the reference category (odds ratio = 1.0) in each study. For details, see text.

† Number of estimates from single studies.

Eleven studies provided confounder-adjusted estimates (2–4, 7–9, 15, 16, 19, 21). However, the adjusted odds ratios were calculated using different reference categories for birth weight. Moreover, nearly every study used a different set of confounders to calculate an adjusted estimate (see table 2 for details). Furthermore, only two studies (4, 7) provided estimates which were adjusted for gestational age (25). Therefore, a meaningful pooled adjusted estimate could not be calculated in this meta-analysis. Consequently, we cannot provide a conclusion on the impact of confounders on the relation between birth weight and type 2 diabetes.

The mechanisms by which birth weight might be related to risk of type 2 diabetes are still a matter of debate. Barker et al. (1) and Hales (5) have claimed that the relation between low birth weight and type 2 diabetes risk reflects long-term consequences of in-utero undernutrition. The initial studies by Barker, Hales, and colleagues indicated that these associations were attributable to selective survival during historical periods with exceptionally high perinatal mortality (26). Interestingly, however, as particularly underlined by meta-regression and categorical analysis in our study, the relation between birth weight and risk of type 2 diabetes also exists within the normal range of birth weight. Notably, however, Hofman et al. (27) provided data clearly contradicting prenatal undernutrition as a causal factor for the ''small baby syndrome.'' They demonstrated that full-term small-for-gestational-age infants are as insulin-resistant later in life as preterm appropriate-for-gestational-age children. While low birth weight in full-term small-for-gestational-age infants might hypothetically be caused by undernutrition in utero, this cannot be the case in preterm appropriate-for-gestational-age children (25). Consequently, the pathophysiologic agent that causes increased risk in low birth weight babies is unlikely to be prenatal undernutrition. Rather, these and other data point toward a role of the neonatal environment in the association between low birth weight and type 2 diabetes. In

particular, low birth weight babies are highly likely to be subjected to neonatal overfeeding, leading to rapid neonatal weight gain, which is positively related to adult overweight (28, 29). Overweight and obesity, however, are known to be the main risk factors for type 2 diabetes. These epidemiologic findings are supported by animal studies which indicate that neonatal overnutrition leads to rapid neonatal weight gain, which is followed by excess weight and diabetogenic disturbances throughout life (30). Data from our group and others indicate that such neonatal overfeeding, even independent of birth weight, might lead to ''malprogramming'' of neuroendocrine circuits in the mediobasal hypothalamus, which regulate appetite control, body weight, and metabolism (30).

Moreover, the association between high birth weight and increased risk of type 2 diabetes may also reflect, at least in part, perinatal ''malprogramming'' due to exposure to undiagnosed and nontreated maternal hyperglycemia during pregnancy and/or maternal overweight during pregnancy. Maternal hyperglycemia during pregnancy leads to increased fetal insulin levels, resulting in fetal and neonatal macrosomia (31). Given the high prevalences of diabetes and overweight among women of reproductive age in industrialized countries, this may decisively contribute to the increasing frequency of high birth weight. Epidemiologic (31, 32) and experimental (33, 34) studies have shown that offspring of mothers who have diabetes during pregnancy have an increased risk of developing type 2 diabetes, which may be causally linked to fetal hyperinsulinism (35).

Taken together, our results indicate that birth weight is related in a U-shaped manner to later risk of type 2 diabetes. High birth weight was found to be associated with increased risk of type 2 diabetes in later life to the same extent as low birth weight. For the development of causal strategies for primary prevention, more research is urgently needed to uncover the etiopathogenic mechanisms behind this association.

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Conflict of interest: none declared.

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