Meta- and Pooled Analyses

Birth Weight, Early Weight Gain, and Subsequent Risk of Type 1 Diabetes: Systematic Review and Meta-Analysis

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Previous studies suggest that birth weight and weight gain during the first year of life are related to later risk of type 1 diabetes. The authors performed a systematic review and meta-analysis on these associations. Twelve studies involving 2,398,150 persons of whom 7,491 had type 1 diabetes provided odds ratios and 95% confidence intervals of type 1 diabetes associated with birth weight. Four studies provided data on weight and/or weight gain during the first year of life. High birth weight (>4,000 g) was associated with increased risk of type 1 diabetes (odds ratio = 1.17, 95% confidence interval (CI): 1.09, 1.26). According to sensitivity analysis, this result was not influenced by particular study characteristics. The pooled confounder-adjusted estimate was 1.43 (95% CI: 1.11, 1.85). No heterogeneity was found ($I^2 = 0\%$) and no publication bias. Low birth weight (<2,500 g) was associated with a nonsignificantly decreased risk of type 1 diabetes (odds ratio = 0.82, 95% CI: 0.54, 1.23). Each 1,000-g increase in birth weight was associated with a 7% increase in type 1 diabetes risk. In all studies, patients with type 1 diabetes showed increased weight gain during the first year of life, compared with controls. This meta-analysis indicates that high birth weight and increased early weight gain are risk factors for type 1 diabetes.

birth weight; diabetes mellitus, type 1; meta-analysis; weight gain

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

During recent years, the incidence of type 1 diabetes has increased in many countries worldwide (1, 2). New measures of primary prevention are therefore urgently needed. It has been suggested that environmental factors operating during prenatal life might influence the risk of type 1 diabetes (3). The identification of such risk factors, as well as markers of increased risk, might ultimately lead to the development of new measures of primary prevention of type 1 diabetes, and they might have far-reaching consequences for public health policies.

Interestingly, studies have shown that high birth weight is followed by an increased risk of type 1 diabetes in later life (4–6). Moreover, the association between increased prenatal weight gain and risk of type 1 diabetes appears to be prolonged into early infancy: Studies indicate that rapid weight gain during the first year of life is a risk factor for type 1 diabetes (7, 8). On the contrary, it has been proposed that low birth weight, which was shown to be a risk factor for type 2 diabetes (9, 10), is also associated with an increased risk of type 1 diabetes (11).

By performing a systematic review and meta-analysis, we therefore aimed to quantitatively summarize the currently published evidence on these issues.

MATERIALS AND METHODS

Study base

The systematic review and meta-analysis were conducted according to the Meta-analysis of Observational Studies in Epidemiology (referred to as “MOOSE”) Group checklist (12). This consensus statement was developed to provide uniform guidance for the conduct of meta-analysis of observational studies, in order to increase their quality. It includes...
a checklist on how to obtain the data, perform the analysis, and report the findings of such meta-analyses. We performed a literature search including the databases MEDLINE (1966–2007) and EMBASE (1989–2007), using the terms “birth weight,” “type 1 diabetes,” “insulin-dependent diabetes mellitus,” “IDDM” [insulin-dependent diabetes mellitus], and “juvenile onset diabetes” in the full-text option, without language restrictions. Furthermore, a manual search was carried out of all references cited in original studies and in all reviews identified. To be eligible for inclusion, studies had to fulfill the following criteria: 1) The study had to be an original report investigating the association between birth weight and type 1 diabetes in later life. 2) An odds ratio and 95% confidence interval (or data to calculate them) of type 1 diabetes in at least 2 strata of birth weight had to have been reported. 3) Alternatively, an odds ratio (95% confidence interval) for change in risk of type 1 diabetes per unit of change in birth weight had to have been given. 4) Alternatively, data on body weight and/or weight gain during the first year of life had to have been reported.

From all eligible studies, data were abstracted in duplicate, by using a standardized form.

**Statistical analysis**

We used 3 different approaches to investigate by means of meta-analytical techniques whether an association exists between birth weight and risk of type 1 diabetes in later life: 1) A birth weight cutoff of 4,000 g (high birth weight) was used to compare the risk of type 1 diabetes below and above this value (dichotomous comparison). 2) A birth weight cutoff of 2,500 g (low birth weight) was used to compare the risk of type 1 diabetes below and above this value. 3) The “pool-first method” (13) was used to combine regression coefficients obtained from the studies (linear trend analysis).

**Dichotomous comparison.** For the dichotomous comparisons, data from each study were extracted on the number of subjects with and without type 1 diabetes above or below the cutoff value. By use of these data, corresponding crude odds ratios and 95% confidence intervals were calculated. We calculated a fixed-effects model and a random-effects model to estimate the pooled odds ratios and corresponding 95% confidence intervals across all studies included for risk of type 1 diabetes above versus below the respective cutoff value.

**Linear trend analysis.** In order to quantify a possible dose-response relation between birth weight and risk of type 1 diabetes, we applied the “pool-first method” to all studies that provided data for more than 2 categories of birth weight (13). After visual inspection of the plots for ascertainment of model adequacy, a study-specific regression coefficient and corresponding 95% confidence interval were calculated for each study by using a log-linear model. After exponentiation, the resulting odds ratios and 95% confidence intervals for change in risk for each 1,000-g increase in birth weight were pooled by using a random-effects model.

**Meta-regression analysis.** To investigate the possible presence of a cohort effect, we performed a weighted meta-regression analysis (random-effects model) with year of birth as covariate.

**Assessment of heterogeneity.** Heterogeneity of study results was assessed by 2 methods. First, a Cochrane Q-based test was performed. Second, the I² was calculated, as proposed by Higgins et al. (14). I², ranging from 0% to 100%, is a direct measure of inconsistency of study results in a meta-analysis, with 0% indicating no inconsistency.

**Sensitivity analysis.** For sensitivity analysis, 4 different subgroup analyses were performed. First, we calculated separate estimates for case-control and cohort studies. Second, we stratified the studies according to percentage of participants with missing data (<20% vs. ≥20%). Third, sub-group estimates were calculated according to the method of obtaining data on birth weight (registry vs. records). Fourth, this approach was applied to the methods that were used to obtain the diagnosis of type 1 diabetes (registry vs. records). For all analyses, a random-effects model was used.

**Influence analysis.** Robustness of the pooled estimate was checked by influence analysis, by using a random-effects model: Each of the study estimates was individually omitted from the data set, followed in each case by recalculation of the pooled estimate of the remaining studies.

**Analysis of confounder-adjusted data.** We additionally calculated a pooled odds ratio (95% confidence interval) for the risk of type 1 diabetes resulting from high birth weight (>4,000 g) of all the confounder-adjusted estimates provided in the publications.

**Publication bias.** Publication bias was assessed by inspection of the funnel plot and formal testing for funnel plot asymmetry by using Begg’s test and Egger’s test.

**Software.** All calculations were performed with STATA, version 8, software (Stata Corporation, College Station, Texas).

**RESULTS**

**Birth weight and risk of type 1 diabetes**

Eleven original reports provided data to investigate the association between birth weight and risk of type 1 diabetes (4–6, 11, 15–21). One report consisted of 2 studies (6), so that 12 studies (10 case-control studies, 2 cohort studies) involving a total of 2,398,150 individuals of whom 7,491 had type 1 diabetes were included in the systematic review and meta-analysis on birth weight and type 1 diabetes. Study characteristics are displayed in Table 1.

**High birth weight and risk of type 1 diabetes.** Ten studies provided data for calculation of odds ratios (95% confidence intervals) of type 1 diabetes in subjects with high birth weight (>4,000 g), compared with those below this cutoff value. Figure 1A shows the forest plot with odds ratios and 95% confidence intervals and the pooled estimate for risk of type 1 diabetes in subjects with a birth weight above 4,000 g compared with those in subjects with a birth weight equal to or below 4,000 g (referent). High birth weight was associated with increased risk of type 1 diabetes. The effect size was identical when the fixed-effects model (odds ratio (OR) = 1.17, 95% confidence interval (CI): 1.09, 1.26) was used. Remarkably, no significant heterogeneity was observed.
### Table 1. Characteristics of 12 Studies in a Meta-Analysis of Birth Weight and Risk of Type 1 Diabetes, 1966–2007

<table>
<thead>
<tr>
<th>Authors, Year, and Reference</th>
<th>Country</th>
<th>Study Design</th>
<th>Year of Birth</th>
<th>Age, years</th>
<th>Participants With Missing Data, %a</th>
<th>Final Study Size, no.</th>
<th>Cases With Type 1 Diabetes, no.</th>
<th>Assessment of Birth Weight</th>
<th>Assessment of Type 1 Diabetes</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardwell et al., 2005 (18)</td>
<td>Great Britain</td>
<td>Cohort study</td>
<td>1971–1986</td>
<td>&lt;15</td>
<td>6</td>
<td>447,663</td>
<td>991</td>
<td>Records</td>
<td>Registry</td>
<td>Maternal age, birth order, year of birth, gestational age</td>
</tr>
<tr>
<td>Dahlquist et al., 1999 (19)</td>
<td>Austria, Latvia, Lithuania, Luxembourg, Romania, Bulgaria, Great Britain</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>&lt;15</td>
<td>27</td>
<td>3,183</td>
<td>892</td>
<td>Records</td>
<td>Registry</td>
<td>Maternal age, preeclampsia, short birth length, respiratory disease, jaundice</td>
</tr>
<tr>
<td>Haynes et al., 2007 (20)</td>
<td>Australia</td>
<td>Case-control study</td>
<td>1980–2002</td>
<td>&lt;15</td>
<td>1.5b</td>
<td>558,633</td>
<td>926</td>
<td>Registry</td>
<td>Records</td>
<td>Maternal age, gestational age, birth order, year of birth</td>
</tr>
<tr>
<td>Jones et al., 1998 (5)</td>
<td>Great Britain</td>
<td>Case-control study</td>
<td>1965–1986</td>
<td>&lt;20</td>
<td>1.4</td>
<td>1,815</td>
<td>315</td>
<td>Records</td>
<td>Records</td>
<td>Not tested</td>
</tr>
<tr>
<td>Lawler-Heavner et al., 1994 (21)</td>
<td>United States</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>&lt;18</td>
<td>Not reported</td>
<td>418</td>
<td>221</td>
<td>Questionnaires, records</td>
<td>Registry</td>
<td>Sex, mother’s education, place and year of birth</td>
</tr>
<tr>
<td>McKinney et al., 1999 (16)</td>
<td>Great Britain</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>&lt;16</td>
<td>7.3</td>
<td>515</td>
<td>193</td>
<td>Records</td>
<td>Registry</td>
<td>Not tested</td>
</tr>
<tr>
<td>Patterson et al., 1994 (I) (6)</td>
<td>Great Britain</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>&lt;15</td>
<td>21</td>
<td>1,626</td>
<td>271</td>
<td>Records</td>
<td>Registry</td>
<td>Not tested</td>
</tr>
<tr>
<td>Patterson et al., 1994 (II) (6)</td>
<td>Great Britain</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>&lt;15</td>
<td>5.1</td>
<td>1,548</td>
<td>258</td>
<td>Records</td>
<td>Registry</td>
<td>Not tested</td>
</tr>
<tr>
<td>Stene et al., 2001 (4)</td>
<td>Norway</td>
<td>Cohort study</td>
<td>1974–1998</td>
<td>≤15</td>
<td>0.4</td>
<td>1,376,995</td>
<td>1,821</td>
<td>Registry</td>
<td>Registry</td>
<td>Sex, maternal age, cesarean section, preeclampsia, date of birth</td>
</tr>
<tr>
<td>Stene et al., 2004 (11)</td>
<td>Norway</td>
<td>Case-control study</td>
<td>1985–1999</td>
<td>&lt;15</td>
<td>42</td>
<td>2,160</td>
<td>534</td>
<td>Registry</td>
<td>Registry</td>
<td>Age, sex, place of birth, family history of type 1 diabetes, maternal age, birth order, gestational age, cesarean section, preeclampsia, breastfeeding, maternal education, eczema, allergy, asthma</td>
</tr>
<tr>
<td>Tai et al., 1998 (17)</td>
<td>Taiwan</td>
<td>Case-control study</td>
<td>1984–1993</td>
<td>8.3 (3.3)c</td>
<td>21</td>
<td>391</td>
<td>117</td>
<td>Interview</td>
<td>Registry</td>
<td>Sex, age</td>
</tr>
</tbody>
</table>

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*The reasons for missing data were the following: missing birth weight, lost to follow-up (cohort studies), and no link to registry.

b Cases only.

c Mean (standard deviation).
Moreover, the $I^2$ indicated that null percentage of total variation across studies was due to heterogeneity. Influence analysis (random-effects model) showed that the pooled estimate was very robust: Omission of individual study estimates led to pooled odds ratios ranging between 1.14 (95% CI: 1.05, 1.23) and 1.19 (95% CI: 1.10, 1.28).

**Sensitivity analysis.** Neither the method of obtaining data on birth weight (registry vs. records vs. interview) nor the method used to obtain the diagnosis of type 1 diabetes (registry vs. records) had a remarkable influence on the pooled estimate. The results were also not largely influenced by study design (case-control vs. cohort studies). Furthermore, studies with few participants with missing data (<20%) showed an even larger pooled estimate than those with a higher proportion of participants with missing data (>20%) (Table 2).

**Meta-regression.** Meta-regression analysis showed that the effect size was not influenced by year of birth (regression coefficient = $-0.01$, 95% CI: $-0.03$, 0.01), making cohort effects rather unlikely.

**Figure 1.** Odds ratios and 95% confidence intervals for type 1 diabetes in subjects with birth weights $>4,000$ g compared with subjects with birth weights $\leq 4,000$ g (A) and in subjects with birth weights $<2,500$ g compared with subjects with birth weights $\geq 2,500$ g (B). The pooled odds ratios (diamonds) were calculated by means of a random-effects model; 95% confidence intervals are shown in parentheses and as horizontal bars. OR, odds ratio; CI, confidence interval.
Analysis of confounder-adjusted data. In 6 studies, confounder-adjusted estimates for risk of type 1 diabetes after high birth weight (>4,000 g) were reported. Although the number and type of confounders adjusted for considerably differed among the studies, for orientating purposes we calculated an adjusted pooled estimate (Figure 2). By use of the adjusted data, high birth weight was associated with an even more increased risk of type 1 diabetes than in the unadjusted analysis (OR = 1.43, 95% CI: 1.11, 1.85).

Low birth weight and risk of type 1 diabetes. Eight studies gave data for calculation of odds ratios (95% confidence intervals) of type 1 diabetes in subjects with low birth weight (<2,500 g), compared with those above this cutoff. Figure 1B shows the respective forest plot with odds ratios and 95% confidence intervals and the pooled estimate. Low birth weight was associated with a nonsignificantly reduced risk of type 1 diabetes. The pooled effect measure was significant when the fixed-effects model was applied to the data (OR = 0.56, 95% CI: 0.51, 0.61). The single study values were significantly heterogeneous (P < 0.001), with an $I^2$ of 91. However, influence analysis (random-effects model) showed that none of the studies had a particularly strong influence on the pooled estimate. Omission of individual study estimates led to nonsignificant pooled odds ratios ranging between 0.74 (95% CI: 0.52, 1.05) and 0.93 (95% CI: 0.72, 1.20).

Because in both analyses described above the reference category (i.e., ≤4,000 g or ≥2,500 g) included the exposure category of the other analysis, we recalculated both pooled estimates, now using “normal birth weight” (2,500–4,000 g) as the reference category. For high birth weight, the pooled odds ratios for risk of type 1 diabetes changed to 1.19 (95% CI: 1.10, 1.29). For low birth weight, the pooled estimate was 1.02 (95% CI: 0.71, 1.46).

Linear trend analysis. From 9 of the studies, an odds ratio with 95% confidence interval of type 1 diabetes per 1,000-g linear increase in birth weight could be calculated. Each 1,000-g increase in birth weight was found to be associated with a (nonsignificant) 7% increase in risk of type 1 diabetes (OR = 1.07, 95% CI: 0.99, 1.15). Results were significantly heterogeneous (P = 0.02). According to $I^2$, 55% of the variation across studies was due to heterogeneity. Influence analysis showed that omission of the study by Stene et al. (4) changed the pooled odds ratio of 1.10 (95% CI: 1.03, 1.18) toward significance.

### Table 2. High Birth Weight (>4,000 g) and Risk of Type 1 Diabetes—Sensitivity Analysis (Random-Effects Model)

<table>
<thead>
<tr>
<th>Study Characteristic and Category</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort studies</td>
<td>1.17</td>
<td>1.06, 1.29</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>1.17</td>
<td>1.04, 1.32</td>
</tr>
<tr>
<td><strong>Participants with missing data, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>1.19</td>
<td>1.10, 1.29</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1.07</td>
<td>0.88, 1.30</td>
</tr>
<tr>
<td><strong>Assessment of birth weight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registry</td>
<td>1.13</td>
<td>1.04, 1.24</td>
</tr>
<tr>
<td>Records</td>
<td>1.26</td>
<td>1.11, 1.43</td>
</tr>
<tr>
<td>Interview</td>
<td>1.23</td>
<td>0.63, 2.40</td>
</tr>
<tr>
<td><strong>Assessment of type 1 diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registry</td>
<td>1.15</td>
<td>1.06, 1.25</td>
</tr>
<tr>
<td>Records</td>
<td>1.22</td>
<td>1.0, 1.50</td>
</tr>
</tbody>
</table>

### Decreased Risk Increased Risk of Type 1 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardwell et al., 2005 (18)</td>
<td>1.68 (1.30, 2.18)</td>
</tr>
<tr>
<td>Haynes et al., 2007 (20)</td>
<td>1.19 (0.95, 1.49)</td>
</tr>
<tr>
<td>Lawler-Heavner et al., 1994 (21)</td>
<td>1.00 (0.40, 2.50)</td>
</tr>
<tr>
<td>Stene et al., 2001 (4)</td>
<td>2.38 (1.39, 4.07)</td>
</tr>
<tr>
<td>Stene et al., 2004 (11)</td>
<td>1.09 (0.50, 2.39)</td>
</tr>
<tr>
<td>Tai et al., 1998 (17)</td>
<td>1.03 (0.37, 2.87)</td>
</tr>
<tr>
<td>Pooled</td>
<td>1.43 (1.11, 1.85)</td>
</tr>
</tbody>
</table>

Figure 2. Confounder-adjusted odds ratios and 95% confidence intervals for type 1 diabetes in subjects with birth weights >4,000 g compared with subjects with birth weights ≤4,000 g. The pooled odds ratio (diamond) was calculated by means of a random-effects model; 95% confidence intervals are shown in parentheses and as horizontal bars. OR, odds ratio; CI, confidence interval.
**Publication bias.** No evidence of publication bias was found, as indicated by visual inspection of the funnel plot (not shown) and nonsignificant Begg’s test ($P = 0.92$) and Egger’s test ($P = 0.89$).

**Weight gain during the first year of life and risk of type 1 diabetes**

Four studies gave data on the association between weight and/or weight gain in the first year of life and subsequent risk of type 1 diabetes (7, 8, 22, 23). All of them were case-control studies that involved a total of 3,861 individuals, of whom 1,266 had type 1 diabetes. Study characteristics are displayed in Table 3.

In each of these studies, significantly increased weight and/or weight gain during the first year of life was observed to precede the onset of type 1 diabetes. However, the time point of measurement, as well as the parameters used to describe weight gain (standard deviation score, absolute body weight, and so on), largely differed between the studies. Therefore, it was impossible to quantitatively summarize the findings from these studies by meta-analytical techniques. In all studies, however, an increased weight or weight gain was observed at 6–7 months of age in patients with type 1 diabetes, as compared with controls. In 2 studies (7, 8), a significant group difference was detectable already at 1 month of age.

**DISCUSSION**

For years, it has been discussed whether birth weight and/or weight gain in early infancy might be reproducible and reliable risk factors for type 1 diabetes. The results of this meta-analysis indicate that high birth weight is significantly associated with an increased risk of developing type 1 diabetes in later life. Although the effect of a high birth weight is highly consistent over all studies, it has to be considered that the effect size is rather small. Our systematic review further shows that all studies published so far indicate that rapid weight gain during the first year of life is also associated with later type 1 diabetes. However, the number of studies on this topic is limited. By contrast, no data so far indicate that low birth weight and/or slow weight gain during infancy is related to the development of type 1 diabetes later in life. Rather, our meta-analysis even showed that low birth weight is followed by a slightly, nonsignificantly reduced risk of type 1 diabetes.

Previous meta-analyses on associations between birth weight and risk of later diseases revealed a considerable degree of publication bias in respective studies (24). However, this was not the case here: Neither visual inspection of the funnel plot nor formal statistical testing gave any indication of publication bias. Therefore, it can be concluded that the results of this meta-analysis are unlikely to be substantially biased by a selective lack of unpublished studies that had unwanted results.

Studies on the relation between birth weight and later disease are susceptible to recall bias when birth weight data were obtained by interview or questionnaire. In our meta-analysis, we performed a number of sensitivity analyses to find out whether certain study characteristics might have influenced the pooled estimate. Among others, we stratified for method to obtain birth weight. Although, because of the small number of studies, the confidence estimate was wide, studies that used interview or questionnaire data for birth weight had the same pooled effect size as those that used records, thereby speaking against recall bias.

Although the effect was very consistent over nearly all published studies, it cannot be completely excluded that the association between increased birth weight or rapid weight gain in infancy and the later risk of type 1 diabetes observed here can be, at least in part, explained by confounding. Unfortunately, only in 7 studies was adjustment for confounders performed. For orientating purposes, we used the 6 adjusted estimates for high birth weight to calculate a pooled adjusted odds ratio. Remarkably, the pooled adjusted estimate was even stronger than the unadjusted pooled odds ratio and was still statistically significant. However, the value of this analysis is limited because of the fact that, in only 3 of the studies, adjustment for gestational age was performed, leaving the possibility that high birth weight was due to increased gestational age, at least in some of the cases. Moreover, the number and kind of confounders considered differed widely among the studies, ranging from 2 confounders (17) to 14 confounders (11).

Another limitation of our analysis pertains to the fact that all studies performed so far considered only cases of type 1 diabetes that occurred until the age of 20 years, without detailed data on the age at onset. Therefore, it was impossible to infer from the data whether high birth weight rather leads to an earlier manifestation of type 1 diabetes than to an increased overall risk, as proposed by Dahlquist (25). On the other hand, in the majority of cases, type 1 diabetes is diagnosed during childhood.

Moreover, it has to be considered that extreme between-study homogeneity, as observed in our meta-analysis for the association between high birth weight and risk of type 1 diabetes, can be caused by the multiple inclusion of studies that used the same source populations (26). We therefore carefully checked this assumption. In fact, regarding the studies by Stene et al. (4, 11), it cannot be completely excluded that the larger study (4) included some of the cases also used in the smaller one (11). However, the larger one provided even a larger estimate than the smaller one, thereby reducing the possibility of substantial bias.

If the association observed here is causal, the question of which pathophysiologic mechanisms might be responsible is crucial. Gestational diabetes and maternal overweight during pregnancy are the most important risk factors for increased birth weight (27, 28). Remarkably, already 20 years ago Dörner et al. (29–31) suggested that exposure to maternal diabetes during pregnancy, often resulting from gestational overweight, might lead to an increased risk of type 1 diabetes during childhood. Clinical and experimental studies show that maternal/fetal hyperglycemia leads to overstimulation of the fetal pancreatic beta-cells and that this not only is followed by prenatal hyperinsulinism, which causes increased birth weight, but also predisposes to increased susceptibility of the overstimulated beta-cells to processes causing type 1 diabetes (3, 32, 33), probably
Table 3. Characteristics of 4 Studies in a Systematic Review of Body Weight or Weight Gain in the First Year of Life and Risk of Type 1 Diabetes, 1966–2007

<table>
<thead>
<tr>
<th>Authors, Year, and Reference</th>
<th>Country</th>
<th>Study Design</th>
<th>Year of Birth</th>
<th>Age, years</th>
<th>Participants With Missing Data, %a</th>
<th>Final Study Size, no.</th>
<th>Cases With Type 1 Diabetes, no.</th>
<th>Assessment of Weight</th>
<th>Assessment of Type 1 Diabetes</th>
<th>Confounders</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baum et al., 1975 (22)</td>
<td>Great Britain</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>Not reported</td>
<td>115</td>
<td>35</td>
<td>Records</td>
<td>Records</td>
<td>Not tested</td>
<td>Increased mean weight at 6 months (boys) and 12 months (girls) of age in diabetic children, compared with controls</td>
<td></td>
</tr>
<tr>
<td>EURODIAB Substudy 2 Study Group, 2002 (8)</td>
<td>Austria, Latvia, Lithuania, Luxembourg, Great Britain</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>&lt;15</td>
<td>36</td>
<td>1,836</td>
<td>499</td>
<td>Records</td>
<td>Registry</td>
<td>Maternal age, neonatal jaundice, neonatal respiratory infection, vitamin D supplementation, asthma</td>
<td>Increased weight standard deviation score from 1 month after birth; increased body mass index standard deviation score from 6 months after birth</td>
</tr>
<tr>
<td>Hypponen et al., 1999 (7)</td>
<td>Finland</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>&lt;15</td>
<td>Not reported</td>
<td>821</td>
<td>435</td>
<td>Records</td>
<td>Registry</td>
<td>Breastfeeding, age at introduction of solid food, maternal education, maternal age, place of residence, birth order, birth weight, target height</td>
<td>Increased weight at 1 month (111 g, 95% CI: 0, 218) and 7 months (286 g, 95% CI: 123, 450) of age in diabetic girls, compared with controls</td>
</tr>
<tr>
<td>Johansson et al., 1994 (23)</td>
<td>Sweden</td>
<td>Case-control study</td>
<td>Not reported</td>
<td>&lt;15</td>
<td>16</td>
<td>1,089</td>
<td>297</td>
<td>Records</td>
<td>Records</td>
<td>Not tested</td>
<td>Weight gain (change in standard deviation score) was significantly increased between birth and 3, 6, 9, 18, and 30 months of age in diabetic children, compared with controls</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

a The reasons for missing data were the following: missing birth weight and no link to registry.
caused by increased vulnerability to autoimmune responses against the background of basal beta-cell hyperactivity (34). However, another possible explanation for the observed association would be genetic factors that, on the one hand, could cause increased birth weight via maternal diabetes and, on the other hand, could increase the risk of type 1 diabetes in the child. In order to correct for such genetic influences, it would be necessary at least to adjust the analysis for the presence of maternal type 1 diabetes. Unfortunately, so far no study has done so, thereby increasing the need for further investigations in this field.

By means of systematic review, we also observed an association between rapid weight gain during the first year of life and later risk of type 1 diabetes. Although only 4 studies have been published so far, all of them had in common that weight and/or weight gain during the first year of life was higher in patients who subsequently developed type 1 diabetes, as compared with healthy controls. Similar to the situation in children with high birth weight, a biologically plausible cause can be inferred from current knowledge. A considerable number of observational studies found that formula feeding, as compared with breastfeeding, is associated with increased weight gain during the first year of life (35). However, the only randomized trial on this topic came to opposite results (36). Nevertheless, in their observational analysis, these authors confirmed the findings from the other studies, including their own previous report (37), and therefore critically discussed the generalizability of the results of their trial (36). Formula-fed infants have an increased incidence of type 1 diabetes (38). Formula feeding, as compared with breastfeeding, leads to increased insulin secretion during neonatal life (39). Therefore, similar to the exposure to maternal hyperglycemia/overweight in utero, the resulting beta-cell hyperactivity might increase vulnerability to autoimmune processes predisposing to type 1 diabetes (3).

Taken together, this meta-analysis indicates that high birth weight is associated with an increased risk of type 1 diabetes in later life. This also appears to be the case for increased weight gain during the first year of life but, because of the small number of published studies, the evidence is more limited here. Although it cannot be excluded that other factors, such as those related to the genetic basis of type 1 diabetes (40), are responsible for these associations, exposure to maternal diabetes and overweight during pregnancy and formula feeding can be inferred from current literature (3, 31, 33, 38) to be possible biologic mechanisms. Further studies should therefore investigate whether prenatal and neonatal interventions could be beneficial in the primary prevention of later type 1 diabetes.

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