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ARTICLE

Birthweight and the risk of childhood-onset type 1 diabetes: a meta-analysis of observational studies using individual patient data

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Abstract
Aims/hypothesis We investigated whether children who are heavier at birth have an increased risk of type 1 diabetes.
Methods Relevant studies published before February 2009 were identified from literature searches using MEDLINE, Web of Science and EMBASE. Authors of all studies containing relevant data were contacted and asked to provide individual patient data or conduct pre-specified analyses. Risk estimates of type 1 diabetes by category of birthweight were calculated for each study, before and after adjustment for potential confounders. Meta-analysis techniques were then used to derive combined ORs and investigate heterogeneity between studies.
Results Data were available for 29 predominantly European studies (five cohort, 24 case–control studies), including

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12,807 cases of type 1 diabetes. Overall, studies consistently demonstrated that children with birthweight from 3.5 to 4 kg had an increased risk of diabetes of 6% (OR 1.06 [95% CI 1.01–1.11]; p=0.02) and children with birthweight over 4 kg had an increased risk of 10% (OR 1.10 [95% CI 1.04–1.19]; p=0.003), compared with children weighing 3.0 to 3.5 kg at birth. This corresponded to a linear increase in diabetes risk of 3% per 500 g increase in birthweight (OR 1.03 [95% CI 1.00–1.06]; p=0.03). Adjustments for potential confounders such as gestational age, maternal age, birth order, Caesarean section, breastfeeding and maternal diabetes had little effect on these findings.

Conclusions/interpretation Children who are heavier at birth have a significant and consistent, but relatively small increase in risk of type 1 diabetes.

Keywords Birthweight · Epidemiology · Meta-analysis · Risk factors · Type 1 diabetes mellitus

Introduction

Recent global estimates suggest that approximately 70,000 children per year are diagnosed with type 1 diabetes [1]. Worryingly, this incidence rate is almost universally increasing by around 4% annually [2, 3]. Although the aetiology of the disease is largely unknown, these increases within genetically stable populations suggest the role of environmental influences. It has been proposed that events occurring early in life could be of particular importance [4].

Birthweight is associated with various perinatal factors such as maternal age, gestational age, maternal weight and nutritional status, and maternal diseases [5]. High birthweight has been associated with an increased risk of childhood cancers such as leukaemia [6] and brain tumours [7].

Numerous studies have investigated the role of birthweight in childhood-onset type 1 diabetes. The findings of this research seem inconsistent, as some studies have concluded that high birthweight is associated with increased diabetes risk [8] or reduced diabetes risk [9], while others have shown no association with type 1 diabetes risk [10]. Interpretation of these findings is made more difficult because studies have reported associations using many different categorisations of birthweight [8, 11–14], with some [15, 16] only reporting findings for the extremes of birthweight and others [17–21] not reporting their birthweight results in any detail, concentrating instead on other findings. This could lead to reporting bias if the decision to report birthweight findings was influenced by whether or not results were interesting or ‘statistically significant’.

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Finally, many studies had limited power to detect associations with birthweight due to inadequate sample size.

We performed the first meta-analysis using individual patient data to: (1) assess the evidence of an association between birthweight and type 1 diabetes; (2) explore the shape of any association; and (3) adjust the observed association for potential confounders (such as gestational age, maternal age and maternal diabetes).

Methods

Literature search The main literature search was conducted using MEDLINE, through Ovid Online (www.ovid.com). The search strategy used the following terms: ('Birth weight' or birth weight or birthweight) and ('Diabetes Mellitus, Type 1' or [diabetes and Type 1] or IDDM), with the terms in inverted commas used as MEDLINE subject heading key words. Similar searches were conducted on Web of Science (http://apps.isiknowledge.com) and EMBASE (www.embase.com). Finally, to identify studies that investigated birthweight along with other risk factors, a more general search was conducted on MEDLINE using the terms: ('Diabetes Mellitus, Type 1' and ['Case–control Studies' or 'Cohort Studies']). The searches were limited to studies on humans published before July 2009. Abstracts were screened independently by two investigators (C. R. Cardwell, C. C. Patterson) to establish whether the studies were likely to provide relevant data based on the following inclusion criteria: (1) the studies identified a group with type 1 diabetes and a group without type 1 diabetes; and (2) they recorded birthweight in these two groups. Studies were excluded if they contained fewer than 100 cases or if they were family-based (because it is possible that the association between birthweight and diabetes is different in individuals with a higher genetic susceptibility). Citations generated from the more general MEDLINE search were initially screened to remove obviously irrelevant articles. Finally, the reference lists of all pertinent articles were hand-searched and corresponding authors of articles included in the review were asked if they were aware of any additional studies.

The corresponding author of each study included was requested to provide data on the association between birthweight and type 1 diabetes in the following categories: <2.5, 2.5–3.0, 3.0–3.5, 3.5–4.0, ≥4 kg. It was necessary to contact authors because it was generally not possible to extract such data from the published reports, as they reported birthweight using different categorisations or (in some cases) did not report their birthweight data at all. It was also necessary to contact authors to facilitate consistent adjustment of the association with birthweight for the following potential confounders: gestational age, maternal age, birth order, breastfeeding, Caesarean section and maternal diabetes. Authors were requested to provide raw data or to provide adjusted estimates of the association between birthweight and type 1 diabetes after conducting specified additional analyses.

Details of studies included (country, design, year of publication and response rates), participants with type 1 diabetes (source, age at onset) and control participants (source) were extracted by one reviewer (C. R. Cardwell) and confirmed by the corresponding authors of the respective studies.

Statistical analysis Odds ratios and SEs were calculated for the association between diabetes and each category of birthweight for each study. Similarly, to investigate the trend across categories of birthweight, an OR (and SE) was calculated per increase in category (corresponding to approximately 500 g) using regression models appropriate to the design of the study. Unconditional and conditional logistic regression analyses were used to calculate ORs and SEs for the unmatched and matched case–control studies, respectively. In cohort studies with varying duration of participant follow-up, rate ratios and their SEs were used instead of ORs, which were not directly calculable. As type 1 diabetes is a rare disease, these measures should be approximately equal [22]. Poisson regression was used to adjust these rate ratios for differences in the year of birth between those developing diabetes and those not, a consequence of this study design, by adding a year of birth term to the regression model in addition to birthweight. Tests for heterogeneity between studies were conducted and random-effects models used to calculate pooled ORs [23]. Random-effects models were deemed more appropriate than fixed-effects models because it was anticipated that between-study heterogeneity would exist, due to the observational nature of studies. The I^2 statistic was calculated to quantify the degree of such heterogeneity [24]. This statistic measures the percentage of total variation across studies due to heterogeneity. Publication/selection bias was investigated by checking for asymmetry in funnel plots of the study ORs against the standard error of the logarithm of the ORs [25].

A two-stage technique was used to calculate pooled estimates of the association between birthweight and diabetes after adjustment for potential confounders [26]. First, adjusted estimates and SEs were calculated within each study using regression models appropriate to the study design (logistic regression for case–control studies, conditional logistic regression for matched case–control studies and Poisson regression for cohort studies); regression models included diabetes as the outcome variable and birthweight and the potential confounder(s) of interest as explanatory variable(s). As explained previously, Poisson regression models additionally included terms to adjust for differences in year of birth between cases and controls in the cohort

studies with varying participant follow-up. Meta-analysis techniques were then applied to these adjusted estimates.

Sub-group analyses were conducted subdividing studies by type (case–control and cohort) and including only studies with a low risk of bias (excluding case–control studies in which controls were not population-based or not randomly selected controls, and excluding any study with a response rate of less than 80% in the case group or control group). A separate analysis was conducted by age at onset of diabetes.

All statistical analyses were performed using STATA 9.0 (Stata, College Station, TX, USA).

Results

Search results The searches identified 81 relevant articles. Of these, 35 were excluded because they contained duplicate or overlapping information; only the most comprehensive article was retained in the review. Ten articles were excluded because they contained information on fewer than 100 cases, six articles were excluded because they had family-based designs and a further article was excluded (after contact with the author) because birthweight was not recorded in sufficient detail [27]. A full list of the papers identified by the searches is available from the authors.

The remaining 29 articles [8–13, 15–19, 21, 28–44] contained information from 34 independent studies, as information from five centres was taken from one article [15] and information from two centres was taken from another [19]. An investigator from each of the 34 studies was invited to provide raw data (or estimates from pre-specified analyses), but one author [40] could not be contacted. Individual patient data or pre-specified estimates were obtained from 29 studies (in one study [28], data were extracted directly from the published report). Characteristics of these predominantly European studies are shown in Table 1.

Birthweight and type 1 diabetes The association between birthweight and type 1 diabetes from these 29 included studies (with a total of 12,087 cases of type 1 diabetes) is shown in Fig. 1. Overall, children with higher birthweights had small increases in their risk of type 1 diabetes. Specifically, children weighing 3.5 to 4.0 kg at birth had on average a 6% increase and children born heavier than 4.0 kg had on average a 10% increase in their risk of diabetes (p=0.02 and p=0.003, respectively); there was little heterogeneity in these increases between studies (I^2=0, p=0.70 for heterogeneity and I^2=0, p=0.94 for heterogeneity, respectively). No difference in the risk of diabetes was found in children weighing 2.5 to 3.0 kg at birth (combined OR 1.01, p=0.82) compared with children of 3.0 to 3.5 kg birthweight. There was also no difference in the risk of diabetes in children born lighter than 2.5 kg (combined OR 0.98, p=0.75); however, we did find evidence of marked heterogeneity between studies for this association (p=0.01 for heterogeneity, I^2=42). Figure 1 shows that this heterogeneity was partly due to the study designs. Cohort studies consistently (p=0.64 for heterogeneity, I^2=0) demonstrated a reduced risk of diabetes in children born lighter than 2.5 kg (combined OR 0.79, p=0.002), while case–control studies were less consistent (p=0.03 for heterogeneity, I^2=38) and found no evidence of reduced risk of diabetes in children born lighter than 2.5 kg (combined OR 1.07, p=0.45). Finally, funnel plots of the association between birthweight in categories and risk of type 1 diabetes (Electronic supplementary material [ESM] Fig. 1) roughly conformed to the expected funnel shape, providing little evidence of asymmetry and therefore little evidence of publication bias. Further analysis comparing children weighing over 4 kg at birth with children weighing under 4 kg revealed a combined OR of 1.09 (95% CI 1.02–1.15; p=0.006); for children weighing under 2.5 kg at birth vs those weighing over 2.5 kg, the combined OR was 0.93 (95% CI 0.80–1.08; p=0.32).

A linear trend in the risk of type 1 diabetes per category increase in birthweight (corresponding to approximately 500 g) was also investigated (Table 2). Although we found evidence (p=0.03) of a linear increase in the risk of diabetes by on average 3% per 500 g, this was subject to heterogeneity (I^2=35%, p=0.03); moreover, Fig. 1 revealed a number of studies [9, 18, 31, 43] which did not seem to conform to a linear trend.

Adjustments for potential confounders Table 2 shows the overall results for birthweight before and after adjustments for potential confounders. The results after adjustment for maternal age, gestational age and birth order are largely consistent with the unadjusted results, except that the overall OR in the under 2.5 kg category is slightly reduced (adjusted OR 0.87); consequently the OR per 500 g increase is slightly increased (adjusted OR 1.05). The fully adjusted results, which were additionally adjusted for breastfeeding, Caesarean section and maternal diabetes (information on available confounders, see Table 1), are also shown and differed only slightly (Table 2). Repeating the analysis after removal of children born to mothers with diabetes in the 20 studies with available data had little impact on the association between birthweight and type 1 diabetes (data not shown).

Analysis by study quality Table 2 also contains an analysis in 12 studies with a low risk of bias (excluding case–control studies with non-population based or not randomly selected controls, and excluding any study with a response rate of less than 80% in the case or control group, as shown in Table 1). In these 12 studies, a slightly more marked association between birthweight and type 1 diabetes was seen. Thus compared with the 3.0 to 3.5 kg birthweight

Table 1 Characteristics of included studies investigating the association between birthweight and type 1 diabetes, ordered by publication date

Study			Type 1 diabetes					Controls			Available confounders[d]					
First author [ref]	Design	Country	Source	Year of diag	Age at diag. (years) [a]	n (<5years)[b]	R[c]	Source (matching criteria)	n[b]	R[c]	GA	MA	BO	CS	MD[h]	BF[i]
Patterson [16]	C-C	UK	Hosp. admission/childhood diabetes register	1976–1988	0–14	268 (73)	100	Maternal discharge records (age, sex, area)	1340	100	✓	✓	✓	✓	✓0.4	
Lawler-Heavner [28]	C-C	USA	Colorado IDDM registry	1978–1988	<18	221	?	Newspapers/radio/posters[f]	197	?						
Bock [10]	C-C	Denmark	Hosp. admission, National Patient Registry	1978–1989	<16	837	98	Birth registry (age, sex)	837	NA						
Wadsworth [31]	C-C	UK	British Paediatric Association surveillance unit	1992	0–5	214 (214)	89	Health Authority Immunization Register	318	70		✓	✓		✓1.9	✓4
Gimeno [32]	C-C	Brazil	Diabetes Association\ Hospital admission	1995	0–19	333 (105)	91	Unclear (neighbourhood, sex, age)[f]	333	100		✓	✓		✓0.3	✓3
McKinney [13]	C-C	UK	Yorkshire Childhood Diabetes Register	1993–1994	0–15	214 (43)	94	GPs' records (age, sex)	423	82	✓	✓	✓	✓	✓0	✓any
Rami [34]	C-C	Austria	Vienna type 1 diabetes register	1989–1994	0–14	103 (14)	86	Schools (age, sex)	373	80	✓	✓	✓	✓	✓0.3[d]	✓any
Eurodiab [15]	C-C	Bulgaria	W. Bulgaria type 1 diabetes register	1991–1994	0–14	127 (34)	73	Schools, polyclinics (age)	440	79	✓	✓	✓	✓	✓0.5[d]	✓any
	C-C	Latvia	Latvian type 1 diabetes register	1989–1994	0–14	133 (24)	99	Population register (age)	301	79	✓	✓	✓	✓	✓0.3[d]	✓any
	C-C	Lithuania	Lithuanian type 1 diabetes register	1989–1994	0–14	115 (36)	94	Polyclinics (age)	266	73	✓	✓	✓	✓	✓0[d]	✓any
	C-C	L'bourg	L'bourg type 1 diabetes register	1989–1995	0–14	57 (15)	100	Pre-schools and schools (age)	172	95	✓	✓	✓	✓	✓0[d]	✓any
	C-C	Romania	Bucharest type 1 diabetes register	1989–1994	0–14	82 (14)	74	Pre-schools and schools (age)	277	81	✓	✓	✓	✓	✓0[d]	✓any
Stene [8]	Co	Norway	Norwegian Childhood Diabetes Registry	1989–1998	0–14	1,810 (376)	100[g]	Norwegian medical birth registry	1,382,602	NA	✓	✓	✓	✓	✓0.4	
Visalli [21]	C-C	Italy	Lazio type 1 diabetes register	1989–1995	0–14	141 (19)	100	Schools (age)	703	91	✓	✓		✓	✓0.5	✓3
Stene [36]	C-C	Norway	Norwegian Childhood Diabetes Registry	1989–2000	0–14	346 (58)	73	Norwegian population registry	1,626	56	✓	✓	✓	✓	✓0.2[d]	✓3
Sadauskaite-Kuehne [19]	C-C	Sweden	S.E. Sweden type 1 diabetes register	1995–2000	0–15	492 (98)	100	Population register	1084	73	✓	✓	✓		✓0.5[d]	✓3
	C-C	Lithuania	Lithuanian type 1 diabetes register	1996–2000	0–15	284 (42)	100	Outpatient clinic[f]	807	95	✓	✓	✓		✓0.3[d]	✓3
Marshall [17]	C-C	UK	Morecombe Bay\E. Lancashire diabetes clinics	1998	0–15	196 (78)	83	Health Authorities (sex, birth date)	381	53	✓	✓	✓		✓0.5[d]	✓any
Cardwell [11]	Co	UK	N. Ireland type 1 diabetes register	1971–2001	0–14	984 (188)	92[g]	Northern Ireland Child Health Register	439,647	NA	✓	✓	✓	✓	✓0.2	✓any
Sipetic [37]	C-C	Serbia	Belgrade hospital admission	1994–1997	0–16	105 (19)	91	Hospital outpatients with skin disease[f] (age, sex, area)	210	100	✓	✓	✓	✓	✓1.0[d]	✓4
Svensson [38]	C-C	Denmark	Danish register of childhood diabetes	1996–1999	0–14	474 (118)	81	Danish population register (age, sex)	674	48	✓	✓	✓	✓	✓1.5	✓4
Malcova [39]	C-C	Cz. Rep.	Czech Childhood Diabetes Register	1987–2000	0–14	850 (195)	76	School friends[f]	1,458	73	✓	✓	✓	✓	✓0.8	✓4
Polanska [18]	C-C	Poland	Upper Silesia Diabetes Register	1986–1996	0–14	344 (49)	87	Central Bureau for Statistics	994,460	100		✓	✓			
Wei [9]	C-C	Taiwan	School-based urine screening programme + questionnaire	1992–1997	0–18	277 (19)	87	Randomly selected negatives from screening programme	533	88	✓	✓	✓		✓0.6	✓3

Table 1 (continued)

Study			Type 1 diabetes					Controls			Available confounders[d]					
First author [ref]	Design	Country	Source	Year of diag	Age at diag. (years) [a]	n (<5years)[b]	R[c]	Source (matching criteria)	n[b]	R[c]	GA	MA	BO	CS	MD[h]	BF[i]
Haynes [41]	Co	Austr.	W. Australian Children's Diabetes Register	1980–2002	0–14	926	99[g]	W. Australia Midwives' Notification System	≈557,707	NA	✓	✓	✓		✓0.1	
Ievins [12]	Co	UK	Hosp. admission (ICD diabetes code)	1963–1999	0–14	408 (100)	?	Oxfordshire/W. Berkshire maternity records	266,665	NA	✓	✓	✓	✓	✓0.7	✓any
Borras Perez [42]	C-C	Spain	Catalonia type 1 diabetes register	1978–2008	0–14	607 (215)	72	Catalonia Public Health Birth Register	3,321	98	✓	✓				✓any
Rosenbauer [43]	C-C	Germany	Nationwide hosp.-based surveillance	1992–1995	0–4	746 (746)	71	Local registration offices (age, sex, area)	1,828	43		✓	✓		✓0.4[d]	✓4
Waldhoer [44]	Co	Austria	Austrian diabetes register	1989–2005	0–5	444 (444)	85[g]	Birth certificate registry	1,435,668	NA	✓	✓	✓			

[a] In years; [b] number included in analysis of birthweight; [c] response rate (%); [d] tick denotes data recorded in study and available for analysis; [e] maternal type 1 diabetes used in analyses; [f] not randomly selected or not population-based; [g] percentage of cases identified in cohort shown in subscript; [h] proportion (%) of controls whose mothers have (type 1) diabetes; [i] duration (months) of breastfeeding used in adjusted analysis shown in subscript

Austr., Australia; BF, breastfeeding; BO, birth order; C-C, case–control; Co, cohort; CS, Caesarean section; Cz. Rep., Czech Republic; GA, gestational age; L'bourg , Luxembourg; MA, maternal age; MD, maternal diabetes; ref, reference

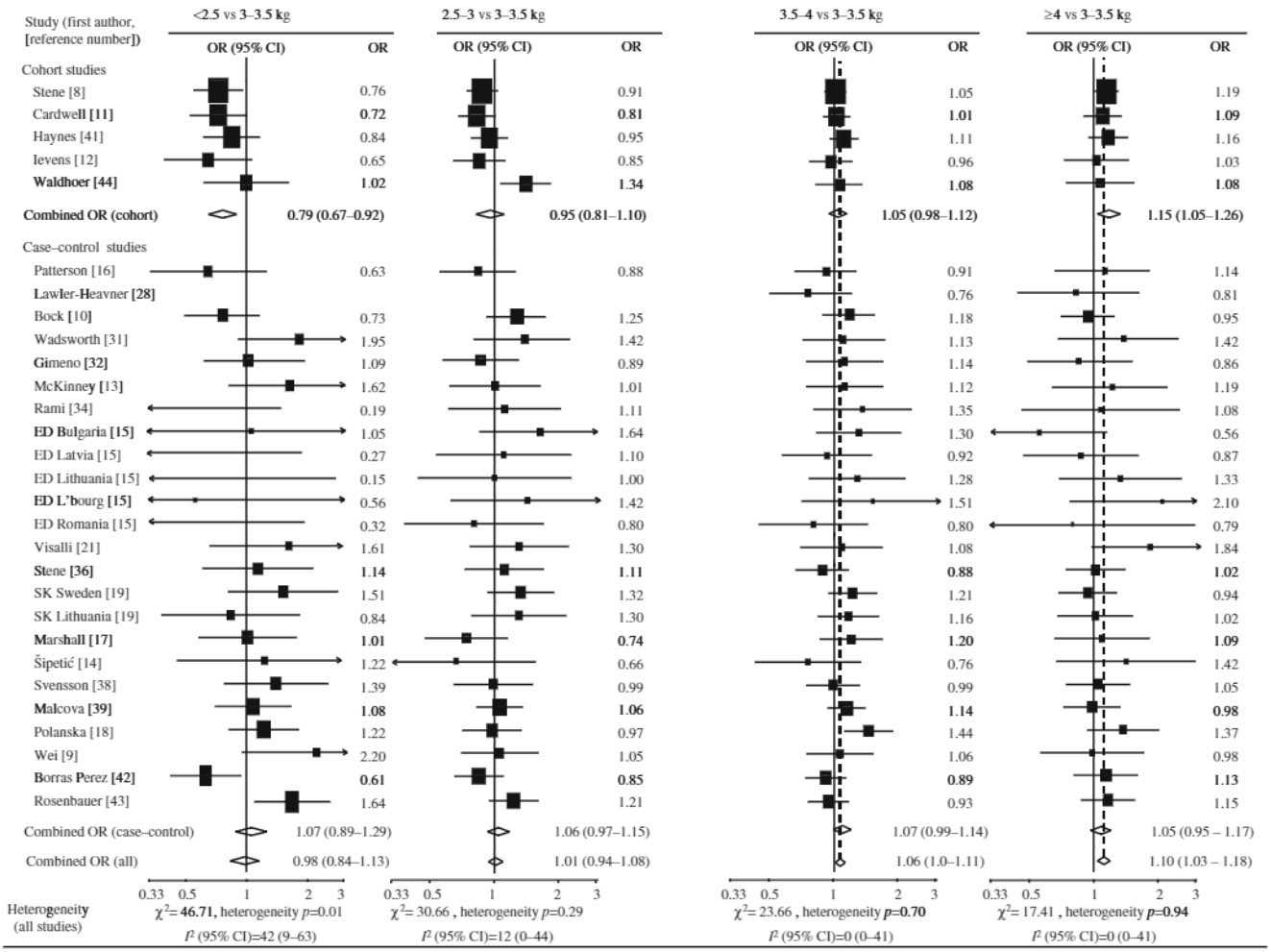

Fig. 1 Meta-analyses of the unadjusted association between birthweight in categories (compared with reference category 3–3.5 kg) and type 1 diabetes including 12,087 cases) using the random effects model, studies ordered by publication date. L'bourg, Luxembourg

category, the increase in diabetes risk in children of 3.5 to 4.0 kg birthweight was 9%, while that in children born heavier than 4.0 kg was 16%. These studies also showed a more marked increase in diabetes risk per 500 g increase in birthweight, namely 7%, with considerably less heterogeneity in their estimates (I^2=12%, p=0.32).

Analysis by age at onset There was little evidence of a difference in the association between birthweight and type 1 diabetes in early-onset (age under 5 years) cases and later onset (age over 5 years) cases in the 23 studies in which these data were available. For instance, per 500 g increase in birthweight, there was a 4% (OR 1.04 [95% CI 0.99–1.09]) increase in early-onset and a 4% (OR 1.04 [95% CI 1.01–1.08]) increase in later onset disease.

Other studies In five of the studies identified by our searches [29, 30, 33, 35, 40] the required data could not be obtained from authors (or extracted from the published reports). In a Swedish study [30] (with 4,584 cases of type 1 diabetes) we were able to estimate results from a figure, but only using a different reference category (of 3.0 to 4.0 kg). Recalculating estimates using this reference category in 28 of the studies included (and for which data were available) generated an increased risk of diabetes in children born heavier than 4.0 kg of 8% (combined OR 1.08 [95% CI 1.02–1.15]; p=0.01) compared with children weighing 3.0 to 4.0 kg at birth. After adding this Swedish study, this increase in risk was little altered (combined OR 1.07 [95% CI 1.02–1.12]; p=0.01).

A study from Finland [35] (662 cases) reported an increase in mean birthweight in cases compared with controls in males (3.7 vs 3.6 kg, respectively; p=0.04) and in females (3.6 vs 3.5 kg, respectively; p=0.49). A study from Denmark (with 839 cases) reported no significant difference in birthweight between cases and controls. Finally, two other studies, one from Hungary [29] and one from USA [40], reported little evidence of a difference, but contained relatively few cases (163 and 103, respectively).

Table 2 Meta-analyses of 29 studies investigating the association between birthweight and type 1 diabetes (including 12,087 cases) before and after adjustments for recorded confounders and in studies with low risk of bias

Analysis per birthweight categories (kg)	Cases (*n*)	Combined OR (95% CI)	*p* value	Heterogeneity	
				$\chi 2$ (*p*)	I^2
Unadjusted[a]					
<2.5	554	0.98 (0.84–1.13)	0.75	46.71 (0.01)	42
2.5–3.0	1,713	1.01 (0.94–1.08)	0.82	30.60 (0.29)	12
3.0–3.5	4,399	1.00 (Ref. cat.)			
3.5–4.0	3,849	1.06 (1.01–1.11)	0.02	23.66 (0.70)	0
≥4	1,572	1.10 (1.03–1.18)	0.003	17.41 (0.94)	0
Trend		1.03 (1.00–1.06)	0.03	43.29 (0.03)	35
Adjusted for gestational age, maternal age and birth order (where available)[b]					
<2.5	528	0.87 (0.73–1.04)	0.13	54.62 (0.001)	51
2.5–3.0	1,643	0.98 (0.91–1.07)	0.68	33.76 (0.17)	20
3.0–3.5	4,212	1.00 (Ref. cat.)			
3.5–4.0	3,697	1.07 (1.02–1.13)	0.01	25.92 (0.58)	0
≥4	1,531	1.13 (1.05–1.22)	0.001	30.13 (0.36)	70
Trend		1.05 (1.01–1.08)	0.01	53.76 (0.002)	48
Adjusted for all available confounders as shown in Table 1[c]					
<2.5	517	0.87 (0.73–1.04)	0.13	50.60 (0.004)	47
2.5–3.0	1,600	0.98 (0.90–1.07)	0.67	35.37 (0.13)	24
3.0–3.5	4,127	1.00 (Ref. cat.)			
3.5–4.0	3,617	1.07 (1.02–1.13)	0.009	24.24 (0.67)	0
≥4	1,506	1.11 (1.03–1.20)	0.01	32.02 (0.27)	13
Trend		1.04 (1.01–1.08)	0.01	53.09 (0.003)	47
Unadjusted, including only studies with a low risk of bias (n=12 studies)[d]					
<2.5	284	0.92 (0.75–1.11)	0.37	18.95 (0.06)	42
2.5–3.0	906	1.01 (0.91–1.12)	0.90	14.96 (0.18)	26
3.0–3.5	2,286	1.00 (Ref. cat.)			
3.5–4.0	2,057	1.09 (1.02–1.16)	0.01	8.86 (0.63)	0
≥4	872	1.16 (1.07–1.26)	0.001	6.55 (0.83)	0
Trend		1.07 (1.04–1.10)	<0.001	12.56 (0.32)	12

[a] One study [28] unavailable for the categories <2.5 kg and 2.5–3.0 kg

[b] Adjusted for gestational age in categories (≤37, 38–41, ≥42 weeks), maternal age in categories (<20, 20–24, 25–29, 30–34, ≥35 years) and birth order in categories (1st, 2nd or 3rd born) except for four studies [18, 31, 32, 43] that were not adjusted for gestational age, two studies [21, 42] not adjusted for birth order and two unadjusted studies [10, 28]

[c] Adjusted for maternal age in categories as above, gestational age in categories (as above), birth order in categories (as above), maternal diabetes (see Table 1), Caesarean section (yes or no) and breastfeeding (see Table 1 for details)

[d] Excluding case–control studies with controls not randomly selected or population-based or studies in which the response rate in either the case group or control group was less than 80% (or unknown) as shown in Table 1

Ref cat., reference category

Discussion

This meta-analysis demonstrates a consistent, but relatively small increase in the risk of type 1 diabetes in children who are heavier at birth. This increase in diabetes risk was more marked in studies with a low risk of bias. The association could not be explained by the confounding influence of gestational age, maternal age, birth order, Caesarean section, maternal diabetes or breastfeeding.

The main strength of this meta-analysis is that it used individual patient data (or estimates from pre-specified analyses) from 28 studies, allowing a unified approach to the investigation of birthweight and type 1 diabetes. It also included 12,058 cases, thus providing high power to

identify associations of relatively small magnitude and allowing reliable subgroup analyses.

Although data were not available from five of the 34 studies identified, in the largest of these [30], approximate results could be extracted from a figure and were consistent with our main finding (as demonstrated by sensitivity analysis). Our search strategy was comprehensive, but it is nevertheless possible that other studies containing relevant data were not identified. Such studies, moreover, would have to be large and to have observed markedly different associations to influence our overall findings. Another potential weakness is that the birthweight association could only be adjusted uniformly for gestational age using the categories less than 38 weeks, 38 to 41 weeks and greater than 41 weeks; however, in 11 studies with available and complete gestational age information, the association with birthweight was little altered after adjustments based upon much finer categories (≤36, 37–38, 39, 40, ≥41 weeks).

A previous meta-analysis of birthweight and type 1 diabetes [45] included fewer studies than ours (and based its estimate for high birthweight upon ten studies only, whereas ours was based on 29 studies). Compared with our analysis, that previous work observed a slightly more marked 17% increase in diabetes risk in children weighing over 4.0 kg at birth, relative to children weighing under 4.0 kg (prior to adjustment for confounders). Although reported for 'orientating purposes only' [45, 46], the less comprehensive approach of that previous study to adjustment for various confounders produced a much more marked effect of birthweight, suggesting a 43% increase in diabetes risk (based on six studies). In contrast, our analysis, using individual patient data from 29 studies with no duplicated data [47], demonstrates that confounding by various perinatal factors (such as gestational age, maternal age, birth order, Caesarean section, maternal diabetes or breastfeeding) has little influence on the birthweight association.

The mechanism behind the observed association between birthweight and type 1 diabetes remains unknown. Although our finding for birthweight remained after adjustment for various potential confounders (such as gestational age, maternal age, birth order, breastfeeding, Caesarean section delivery and maternal diabetes), it is impossible, as with all observational studies, to rule out residual confounding and it seems unlikely that birthweight plays a direct causal role. It is more probable that birthweight is a marker for some unknown exposure or exposures that influence type 1 diabetes risk such as maternal nutrition, maternal body weight or maternal diseases [5]. Ethnicity is also a possible confounder, as children born to Asian mothers, who are likely to be lighter at birth [48], also have a lower risk of type 1 diabetes [1]. It seems unlikely, however, that in these predominantly European populations this could explain the entirety of the observed association.

The observed association between type 1 diabetes and birthweight is supported by two animal studies. A recent experimental study in NOD mice demonstrated that calorific restriction during pregnancy resulted in reduced birthweight, leading to reduced risk of diabetes by 24 weeks [49]. Also an observational study in BioBreeding rats demonstrated a higher risk of diabetes with increased birthweight [50]. However, care should be taken when extrapolating animal results for aetiological factors to humans.

As fetal insulin is an important growth factor, children with greater intrauterine growth and consequently higher birthweight have pancreatic beta cells which secrete insulin more actively [51]. In vitro and other evidence shows that actively insulin-secreting beta cells are more prone to destruction via various mechanisms such as susceptibility to interleukin 1-beta and increased levels of islet antigens [52]. Further experimental animal data have been reviewed and potential mechanisms previously discussed [53]. A number of studies have found postnatal body size or growth to be associated with risk of type 1 diabetes [54, 55]. Consequently, it is possible, and worth further investigation, that the observed association between birthweight and type 1 diabetes may somehow be mediated via postnatal growth. It is also possible that some unknown genetic factor predisposes to high birthweight and increased risk of type 1 diabetes. Although one study [56] has demonstrated that established type 1 diabetes high-risk HLA genotypes are associated with higher birthweight in the general population, another [57], which recorded established HLA and insulin gene polymorphisms, demonstrated that the observed association between type 1 diabetes and birthweight was independent of these genetic factors.

Our study suggests that the association between type 1 diabetes and birthweight is similar in children diagnosed under 5 years and in those diagnosed between 5 and 15 years of age. However, the observed association between childhood-onset type 1 diabetes and birthweight may not hold for adult-onset type 1 diabetes, as two large studies [58, 59] investigating type 1 diabetes diagnosed in young adults have shown little evidence of association with birthweight.

In conclusion, children who are heavier at birth have a significant and consistent increase in their risk of type 1 diabetes. However this increase is relatively small in magnitude and suggests that increasing trends in birthweight explain little of the rise in type 1 diabetes incidence currently being observed in many countries [3].

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