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Review Article

Association between childhood obesity and subsequent Type 1 diabetes: a systematic review and meta-analysis

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Abstract

Aims To review and synthesize the published evidence on the possible association between childhood obesity and the subsequent risk of Type 1 diabetes.

Methods The PubMed database was systematically searched for studies using childhood obesity, BMI or %weight-for-height as the exposure variable and subsequent Type 1 diabetes as the outcome. Studies were only included if assessment of obesity preceded the diagnosis of Type 1 diabetes.

Results Eight case–control studies and one cohort study were included, comprising a total of 2658 cases. Of these nine studies, seven reported a significant association between childhood obesity, BMI or %weight-for-height and increased risk for Type 1 diabetes. Meta-analysis of the four studies that reported childhood obesity as a categorical exposure produced a pooled odds ratio of 2.03 (95% CI 1.46–2.80) for subsequent Type 1 diabetes; however, in those studies, age at obesity assessment varied from age 1 to 12 years. A dose–response relationship was supported by a continuous association between childhood BMI and subsequent Type 1 diabetes in a meta-analysis of five studies (pooled odds ratio 1.25 (95%CI 1.04–1.51) per 1 SD higher BMI).

Conclusion There is overall evidence for an association between childhood obesity, or higher BMI, and increased risk of subsequent Type 1 diabetes. Several theories have been proposed for a causal relationship. Reduction in Type 1 diabetes should be considered as a potential additional benefit of preventing childhood obesity.

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Keywords body mass index, obesity, systematic review, Type 1 diabetes

Abbreviations MeSH, Medical Subject Headings; SDS, standard deviation scores

Introduction

Twins studies indicate a joint contribution of genetic and environmental factors to the aetiology of Type 1 diabetes [1,2]. Furthermore, the major relevance of environmental determinants is indicated by the steep rise in Type 1 diabetes incidence in immigrants from lower to higher incidence regions, the differences between genetically identical populations with very different living conditions [3], and by the rising incidence of childhood Type 1 diabetes over several decades in many populations [4,5]. The multi-centre EURODIAB study reported a 3.2% annual increase in Type 1 diabetes incidence among European children from 1989 to 2000 [4], and the DIAMOND study, which collected information on childhood diabetes from 112 centres around the world, found a 2.8% annual increase over the same time period [5]. Many potential 'triggers' for Type 1 diabetes have been investigated, including short duration or lack of breastfeeding, early infancy exposure to cow's milk protein and infections such as enterovirus and rubella [6]. However, none of these associations has yet been proven to be causal.

The suggestion that Type 1 diabetes may be associated with increased weight gain in childhood was first made by Baum and co-workers in 1975 [7]. Baum *et al.* proposed that this might be either attributable to overfeeding or was an early sign of hormonal dysregulation [7]. This observation was revisited when clinicians and epidemiologists noted the simultaneous rise of Type 1 diabetes incidence and childhood overweight and obesity. The International Obesity Task Force estimated that

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during the 1990s the prevalence of childhood overweight increased by 1% per year in Europe, the USA, Canada and Australia [8]. However, in spite of much research and several new hypotheses about the pathogenesis of Type 1 diabetes, the relevance of increased childhood weight gain remains unclear. Data from the Organization for Economic Co-Operation and Development report [9] from 16 wealthy countries does not reveal any obvious relationship between national estimates of childhood obesity prevalence and incidence rates of Type 1 diabetes (Table 1). Therefore, obesity does not account for the wide between-country differences in Type 1 diabetes incidence, which range from 0.57 per 100 000 person-years in China to more than 48 per 100 000 person-years in Sardinia and Finland in the 0- to 14-year age group [10].

A positive association between higher birthweight and Type 1 diabetes risk has been recently demonstrated by meta-analysis [11]. Birthweight is influenced by various maternal, fetal and genetic factors, which may be different from the factors that influence childhood obesity [12]. To our knowledge, there has been no systematic review of the association of childhood obesity and subsequent Type 1 diabetes. We therefore aimed to collate and synthesize the published evidence regarding this prospective association.

Table 1 Relationship between Type 1 diabetes incidence and prevalence of childhood overweight or obesity in 16 Organization for Economic Co-Operation and Development (OECD) countries

Country	Type 1 diabetes incidence rate in children aged 0–14 years (per 100 000 person-years)	% of children aged 11–15 years overweight or obese
Finland	57.4	15.8
Sweden	41.0	10.5
Norway	27.9	10.0
UK	24.5	12.0
Denmark	22.2	9.7
Canada	21.7	21.3
USA	20.8	29.8
Netherlands	18.8	8.0
Germany	18.0	12.0
Ireland	16.3	14.2
Iceland	14.7	14.5
Spain	13.0	16.7
Poland	12.9	11.2
France	12.2	10.5
Greece	9.9	18.8
Italy	8.4	18.3

Figures from *Health at a Glance 2009: OECD Indicators* (9).
There was no evidence for a positive correlation between these country-level estimates of Type 1 diabetes incidence rates in children and the percentage of children overweight or obese ($r = -0.1$).
Childhood overweight and obesity was based on the International Obesity Task Force Criteria (38), and data are from the Health Behaviour in School-Aged Children Surveys taken in 2005 and 2006 in OECD countries (9).
Incidence data and method of ascertainment of Type 1 diabetes were based on the International Diabetes Federation's *Diabetes Atlas*, 4th edition (50).

Methods

Search strategy

A search of published literature was conducted using the PubMed database. The Medical Subject Headings (MeSH) terms 'Obesity', 'Body Weight' and 'Body Mass Index' were combined with the operator 'OR'. The MeSH term 'Diabetes Mellitus, Type 1′ was entered. This term incorporates all terms previously used to describe this disease, including insulin-dependent diabetes, juvenile diabetes and autoimmune diabetes. The MeSH term 'Epidemiologic Studies', which includes the terms 'Case–Control Studies' and 'Cohort Studies', was combined with the term 'Epidemiology' (included as a heading and subheading) using the 'OR' operator. These three elements were combined using the operator 'AND'.

This search identified 1085 titles with publication dates up to February 2010. Further limitation to articles in English or French reduced this number to 968 articles. Abstracts of these articles were read and evaluated on the basis of the inclusion criteria.

Inclusion criteria

Studies from peer-reviewed journals were included if the exposure variable was obesity, BMI or another variable of weight-for-height assessed after birth up to age 18 years, and the outcome was Type 1 diabetes. One article was excluded because it did not adequately distinguish Type 1 diabetes from Type 2 diabetes in the outcome ascertainment.

In addition, in order to fulfill the requirement of temporality, all measurements had to be taken prior to Type 1 diabetes onset. Several studies had explored the related question of whether earlier age of onset of Type 1 diabetes is associated with obesity or BMI status [13–21]. Such studies were excluded because they did not include non-diabetic control groups and they measured obesity status only at the time of Type 1 diabetes onset or later. BMI at Type 1 diabetes onset could be lower as a result of dehydration or acute weight loss, while measurements taken after diagnosis could be increased by the anabolic effects of insulin therapy.

Meta-analysis

For studies reporting results of childhood obesity, or BMI, inverse variance meta-analysis was performed using the 'metan' command in Stata [22]. In the absence of significant heterogeneity between study estimates, a fixed-effects model was chosen. In the presence of significant heterogeneity, a random-effects model was chosen. Analyses were performed using Stata software, release 9 [23].

Results

Eight case–control studies and one cohort study met the inclusion criteria, comprising a total of 2658 cases; details of these studies are shown in Table 2. Six of the eight case–control studies were from Scandinavian countries, which had access to routinely collected historical growth measurements from universal child welfare programmes. Studies differed substantially with regard to age at obesity assessment and the definition of obesity and/or growth references used. Only four studies reported results for childhood obesity as a categorical exposure (Table 3), while other studies reported results for BMI (Table 3) or %weight-for-height (Table 4) as continuous or other categorized exposure variables. Studies also differed according to the use of matching variables to select controls, and also in their choice of covariates (Table 2).

Obesity

All four studies that examined childhood obesity as an exposure [24–27] reported a positive association with Type 1 diabetes. Odds ratios ranged from 1.73 to 3.77 (Table 3). The studies varied in the definition of obesity and the age at measurement. Svensson *et al.* [24] assessed obesity at age 1 year, Viner *et al.* [27] at age 10 years and the EURODIAB study [25] at various ages after age 2 years. Hypponen *et al.* [26] assessed obesity at six different ages from 2 to 12 years; at four of these six time points, the odds ratios for Type 1 diabetes were statistically significant, although the numbers of children declined with increasing age as more case children developed Type 1 diabetes. A meta-analysis was performed on the results of these four studies, giving a pooled odds ratio of 2.03 (95% CI 1.46–2.80) (Fig. 1). This estimate was based on the age 2 years results from Hypponen *et al.* [26], as this was the age group that had the largest sample size (1056 out of 1157 participants had measurements at age 2 years). Sensitivity analyses using results at different ages did not alter the pooled estimate [e.g. using the odds ratio at age 6 years gave a pooled odds ratio of 2.02 (1.50–2.72)]. There was no heterogeneity between the studies (I^2 statistic 0%, $P = 0.4$).

Body mass index

Five studies reported risk of Type 1 diabetes according to childhood BMI as a continuous variable (Table 3) [24,25, 27–29]. All except for Svensson *et al.* [24], which assessed BMI at age 1 year, reported a significant association with Type 1 diabetes. Two studies reported BMI in SD scores (SDS) [25,27] and three in absolute units (kg/m^2) [24,28,29]. Lammi *et al.* [28] took the unique approach of reporting the 'infant maximum BMI' at ages 0–3 years. In order to meta-analyse these results, we converted the reported odds ratios in those studies that described BMI in kg/m^2 to equivalent odds ratios for a 1-SD increase in BMI, using standard deviations for the appropriate ages from the British 1990 growth reference [30]. This gave a pooled odds ratio of 1.25 (95% CI 1.04–1.51) per 1- SD increase in BMI (Fig. 2). There was substantial between-study heterogeneity in the reported estimates ($I^2 = 82.4\%$, $P < 0.001$) and results from the random-effects meta-analysis are therefore reported.

Three further studies reported the mean BMI difference between Type 1 diabetes and control children, expressed in kg/m^2 or SDS (Table 3) [25,29,31]. Again, the studies were inconsistent regarding the ages at which the largest differences were seen. Bruining [31] reported a difference in BMI at 1 year, and the EURODIAB study [25] found significant differences in BMI from ages 6 months to 4 years, with the largest difference being at age 1–2 years. In contrast, Ljungkrantz *et al.* [29] reported a significant difference in BMI between cases and control subjects at ages 5–13 years, but not at earlier ages.

Percent weight-for-height

Three older case-control studies [26,32,33] used %weight-for-height as the exposure variable (Table 4). Hypponen *et al.* [26] used %weight-for-height SDS as a continuous exposure variable and found the differences in relative weight between case and control subjects to be larger at earlier ages (< 3 years) than at ages 3–10 years. The other two studies [32,33] used %weight-for-height in the 4 or 5 years preceding Type 1 diabetes diagnosis as a categorical exposure variable. While Pundziute-Lycka *et al.* [32] reported a significant increase in diabetes risk for children in the top and middle vs. the lowest tertile of %weight-for-height, Blom *et al.* [33] found no difference in Type 1 diabetes risk in children with %weight-for-height above vs. below the mean.

Discussion

Our systematic review has shown that, of nine published studies examining the prospective association between childhood obesity, BMI or %weight-for-height and subsequent Type 1 diabetes, eight reported a significant increased risk, or a positive association, in at least one age group. Meta-analysis of four studies showed that childhood obesity was associated with a roughly twofold increase in the risk of subsequent Type 1 diabetes.

Quality of evidence

Eight of the nine studies used a case–control design, which reflects the infrequency of Type 1 diabetes to be appropriate for most prospective cohort studies. In these studies, recall and information bias was avoided by use of historical child measurement records. Selection bias was avoided by selecting consecutive incident cases from a defined clinic or registry and by using centralized population registers to find appropriately matched controls. All studies but two [29,33] reported participation rates in each group, and these were usually similar between cases and controls. In the one prospective cohort study, by Viner *et al.* [27] based on the 1970 British Birth Cohort Study, BMI was measured only once, at age 10 years.

Table 2 Description of included studies reporting the association between childhood obesity, BMI or %weight-for-height and Type 1 diabetes

Study	Location and year	Study design	Participants	Source of measurements	Growth standard (reference)	Type 1 diabetes diagnosis	Matching/covariates
Blom *et al.* [33]	Sweden 1985–1986	Case–control	337 cases diagnosed age 0–14 years 517 control subjects from Swedish Population Register	Child health clinic	[35]	Physician	Matched by sex, age, region
Bruining [31]	Netherlands 2000	Case–control	91 cases with onset at age 4–15 years 125 healthy siblings of case subjects (50% participation)	Child health clinic	[36] and [37]	Physician	Nil
EURODIAB [25]	Austria, Latvia, Lithuania, Luxembourg, UK 1989–1994	Case–control	499 cases with onset age 0–14 years from population-based registers (73% participation) 1337 control subjects from population-based registers, polyclinics or schools (62% participation)	'Routine records' (not specified)	[30] and [38]	Physician	Distribution matched for age and region. Covariates were maternal age, neonatal jaundice or respiratory infection, vitamin D, asthma, study centre, infant feeding
Hypponen *et al.* [26]	Finland 1986–1989	Case–control	586 cases (94% participation) 571 control subjects from Finnish Population Registry	Child health clinic	[39]	Physician and blood sample for autoantibodies	Matched by sex and birth date. Covariates were height, birth year, birthweight, prematurity, birth order, SES, maternal age, maternal education
Lammi *et al.* [28]	Finland 1992–1996	Case–control	218 cases with onset at age 15–39 years; from Finnish National Healthcare Register (16% participation) 276 control subjects from Finnish National Population Register	Child health clinic	Not necessary	Minimum two data sources (ADA criteria); if unclear C-peptide and autoantibody measurements performed. Non-diabetic status of control subjects also ascertained	Matched by sex, date of birth, birthplace. Further covariate was birthweight
Ljungkrantz *et al.* [29]	Sweden 1995–2000	Case–control	316 cases diagnosed age 0–15 years 1–2 control subjects per case from Swedish Population Register	Child health clinic	[40]	WHO definition	Matched by age and sex
Pundziute-Lycka *et al.* [32]	Sweden 1991–1993	Case–control	74 consecutive patients in a paediatric clinic with onset age 7–14 years (74% participation) 143 control subjects from the Swedish Population Register (72% participation)	Child health clinic	[41]	Physician	Matched by age, sex and neighbourhood

Table 2 (*Continued*)

Study	Location and year	Study design	Participants	Source of measurements	Growth standard (reference)	Type 1 diabetes diagnosis	Matching/covariates
Svensson *et al.* [24]	Denmark 1996–1999	Case–control	490 cases with onset at age 0–14 years from Danish diabetes register (81% participation) 696 control subjects from Danish Population Register (48% participation)	Child health clinic	[42]	Physician	Matched by sex and date of birth. Covariates were maternal age, cohort, gestational age, birthweight, breastfeeding
Viner *et al.* [27]	1970 British cohort	Cohort	8772 participants from an initial cohort of 16 567 47 developed Type 1 diabetes after age 10 years	School medical examination at age 10	[43]	Self-reported 'insulin-dependent diabetes' with age onset age 10–30 years	Birthweight, SES, height z-score at 5 and 10 years, breastfeeding, pubertal status at age 10 years

ADA, American Diabetes Association; SES, socio-economic status; WHO, World Health Organization .

Sixty-one participants reported Type 1 diabetes at age 30 years, but the 14 participants who were diagnosed with Type 1 diabetes before age 10 years were excluded from the analysis. Attrition was also a problem in that study, with the sample size shrinking from 16 567 babies at birth to 8772 adults at age 30 years. Although loss to follow-up was higher in disadvantaged groups, the authors emphasized that follow-up was unrelated to overweight status at age 10 years [27].

Ascertainment of Type 1 diabetes was a potential cause of misclassification bias, particularly for the studies in which diabetes status was determined in individuals over the age of 15 years [27,28], as the prevalence of Type 2 diabetes increases with age. Of these studies, Lammi *et al.* [28] used very strict diagnostic criteria for Type 1 diabetes; however, Viner *et al.* [27] relied on a self-administered questionnaire for outcome ascertainment. Misclassification of obese cases with Type 2 diabetes could falsely exaggerate the association between obesity and Type 1 diabetes.

Several of the case–control studies controlled for age, sex, and region by matching. Only Bruining [31] used healthy siblings as controls. Some studies adjusted for further potential confounders, such as maternal age, birthweight, gestational age, duration of breastfeeding and height, which have been associated with Type 1 diabetes risk. Because of the paucity of studies, we were unable to determine whether adjusted estimates differed substantially from the crude estimates.

Limitations of the systematic review

In addition to the limitations of the individual studies, there were some limitations to our systematic review. Both the meta-analysis of the binary childhood obesity results and the synthesis of results from the other studies were limited by the wide variety of age groups at which the exposure variable was measured. Several studies reported results only for certain age groups and, in some cases, it was difficult to determine whether this was attributable to the study design or whether significant results were preferentially reported. Future collation of individual-level data from the various studies could allow formal exploration of the potential effect of modification by age. With two exceptions [27,28], the studies were restricted to childhood-onset Type 1 diabetes. All identified studies were conducted in European populations and, although not all studies specified the ethnic composition of participants, it is likely that the vast majority of children were of White European origin.

The relevance of obesity to Type 1 diabetes risk in non-European origin children is therefore less clear. The Organisation for Economic Co-Operation and Development analysis relating Type 1 diabetes incidence to obesity prevalence (Table 1) was restricted to European and North American countries. While the prevalence of childhood obesity is rising almost universally, the pattern of Type 1 diabetes incidence varies substantially by country [5]. China has a very low incidence of Type 1 diabetes (0.2–2.3 per 100 000 person-years in children under 15 in 1990–1994), with no obvious

Table 3 Results of studies that reported childhood obesity or BMI as the exposure variable

Exposure	Study	Definition of exposure	Age at measurements	Age at diagnosis (years)	Findings*
Obesity (as a categorical variable)	EURODIAB (25)	IOTF obesity	1–6 months, 1–2, 2–4, 4–6 years (to 1 month before diagnosis)	0–14	OR = 1.73 (1.19–2.52) for obesity after age 2 years
	Hypponen *et al.* (26)	> 120% of % weight-for-height	Birth to 1 year before diagnosis	0–14	OR = 2.35 (0.58, 9.52) at age 2 years OR = 2.37 (1.07, 5.26) at age 4 years OR = 2.10 (1.11, 3.98) at age 6 years OR = 2.36 (1.25, 4.46) at age 8 years OR = 2.25 (1.06, 4.80) at age 10 years OR = 2.96(0.90,9.75) at age 12 years
	Svensson *et al.* (24)	BMI > 2 SD above mean	1 year	0–14	OR = 3.77 (1.41–10.1) at age 1 year
	Viner *et al.* (27)	IOTF obesity	10 years	10–30	HR = 3.1 (1.0–9.3) at age 10 years
BMI (as a continuous variable)	EURODIAB (25)	BMI SDS	1–6 months, 1–2, 2–4, 4–6 years (to 1 months before diagnosis)	0–14	OR 1.35 (1.15–1.57) at age 1–2 years (highest OR was at age 2 years, but significant from ages 6 months to 6 years)
	Lammi *et al.* (28)	Infancy maximum BMI (kg/m^2)	Birth to 3 years	15–39	OR 1.21 (1.05–1.41) at 'infancy maximum BMI'
	Ljungkrantz *et al.* (29)	BMI (kg/m^2)	Birth to 3 months before diagnosis	0–15	OR = 1.19 (1.08–1.31) at age 5 years (no difference before age 3 years, but significant from ages 5–13 years)
	Svensson *et al.* (24)	BMI (kg/m^2)	1 years	0–14	OR = 0.96 (0.88–1.04) at age 1 year
	Viner *et al.* (27)	BMI z-score at age 10 years	10 years	10–30	HR = 1.8 (1.2–2.8) at age 10 years
BMI (mean difference at baseline)	Bruining (31)	BMI SDS	1 year	4–15	Case subjects had significantly higher BMI at 1 year (P = 0.018, numbers not shown)
	EURODIAB (25)	BMI SDS	1–6 months, 1–2, 2–4, 4–6 years (to 1 month before diagnosis)	0–14	+0.08 (–0.06 to 0.23) at age 1–6 months +0.16 (0.00–0.31) at age 6 months–1 year +0.27 (0.10–0.44) at age 1–2 years +0.21 (0.03–0.40) at age 2–4 years 0.20 (–0.01 to 0.41) at age 4–6 years
	Ljungkrantz *et al.* (29)	BMI (kg/m^2)	Birth to 3 months before diagnosis	0–15	+0.69 (0.27–1.11) at age 5 years (case subjects had significantly higher BMI from ages 5 to 13 years)

HR, hazard ratio; IOTF, International Obesity Task Force; OR, odds ratio; SDS, standard deviation score.
*Displayed age is the age at obesity/BMI assessment.

Table 4 Results of studies that reported %weight-for-height as the exposure variable

Study	Definitions of exposure	Age at measurements	Age at diagnosis (years)	Findings
Blom *et al.* (33)	%Weight-for-height SDS (3 groups: ≤ 0, 0–1, ≥ 1 SDS)	1–5 years before diagnosis	0–14	Compared with the reference group (SDS ≤ 0) 0–1 SDS: boys OR = 0.79 (0.50–1.26) 0–1 SDS: girls OR = 0.86 (0.52–1.42) > 1 SDS: boys OR = 0.78 (0.39–1.54) > 1 SDS: girls OR = 0.88 (0.41–1.89)
Hypponen *et al.* (26)	%Weight-for-height SDS (continuous variable)	Birth to 1 years before diagnosis	0–14	10% increase before age 3 years associated with a 50–60% increase risk of Type 1 diabete 10% increase at ages 3–10 years associated with a 20–40% increase risk of Type 1 diabetes
Pundziute-Lycka *et al.* (32)	%Weight-for-height SDS (tertiles)	4 years to 3 months before diagnosis	7–14	OR = 4.09 (1.23–13.63) for top vs. lowest tertile OR = 3.83 (1.19–12.30) for middle vs. lowest tertile

HR, hazard ratio; OR, odds ratio; SDS, standard deviation score.

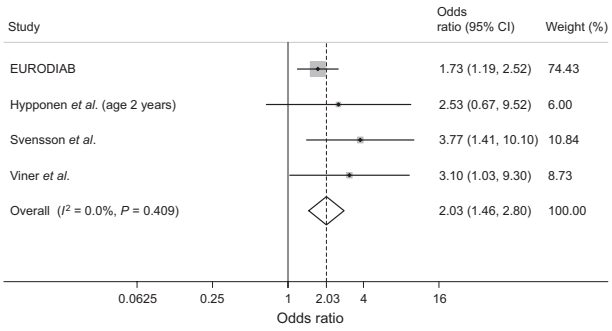

FIGURE 1 Meta-analysis (fixed-effects inverse variance model) of studies of childhood obesity as a risk factor for subsequent Type 1 diabetes.

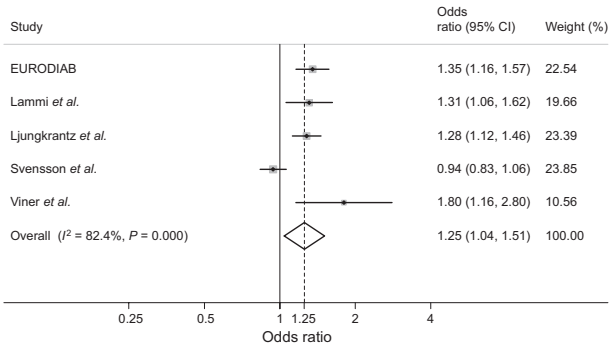

FIGURE 2 Meta-analysis (random-effects inverse variance model) of studies of childhood BMI as a risk factor for subsequent Type 1 diabetes. Odds ratios correspond to a 1-unit increase in BMI standard deviation score (SDS).

secular change [5] despite a marked increase in the prevalence of childhood overweight and obesity from 6 to 16% in a similar period, 1989–1996 [34]. Japan also has a low incidence of Type 1 diabetes (1.4–2.2 per 100 000 person-years in children under 15 in 1990–1993) and this may even be falling [5] despite a rise in childhood overweight and obesity from 7 to 10% from 1974 to 1996 [34]. Similarly in Brazil, the incidence of Type 1 diabetes (7–8 per 100 000 person-years in children under 15 in 1996–1999) appears to be falling [5] despite a rising prevalence of childhood overweight and obesity from 4 to 14% between 1974 and 1997 [34]. There are fewer studies conducted in Africa. In Algeria, where the prevalence of overweight in children aged 6–17 was 6% in 2003, there was a 11.6% annual increase in the incidence of Type 1 diabetes from 1990 to 1999 (overall 8.6 per 100 000 person-years in children under 15) [5]; however, this information was collected from only one region in that country [5]. Kuwait has one of the highest incidence rates of Type 1 diabetes outside of Europe (22.3 per 100 000 person-years in children under 15 in 1992–1999) and is increasing by 7.0% per year (95% CI 3.0–11.1) [5]; notably Kuwait also has a relatively high prevalence of childhood overweight and obesity (15% in children aged 6–10 years) [34]. In summary, while Type 1 diabetes incidence remains low in many non-European origin populations, ongoing surveillance is required to detect possible trends in those settings in response to the nutritional transition to childhood obesity.

Biological plausibility and inferring causation

It has been suggested by several authors [6,33,44] that increased childhood growth and weight gain increases peripheral insulin demand, which could place greater stress on the B-cells and make them more vulnerable to autoimmune attack. This hypothesis is supported by animal models, which show that hyper-functioning B-cells are more susceptible to damage by cytokines [28], and is consistent with the observation in humans that Type 1 diabetes onset often occurs during the pubertal growth spurt when insulin

demand is highest. Alternatively, a genetic predisposition to hyperinsulinaemia could lead to both faster childhood growth and weight gain and increased susceptibility to Type 1 diabetes [28]. The 'Accelerator Hypothesis' of Wilkin [44] takes this idea a step further by proposing that Type 1 diabetes and Type 2 diabetes are the same disease, both triggered by insulin resistance and a predisposition toward B-cell apoptosis, and that they differ only in their speed of onset. However, these hypotheses have not been substantiated by recent studies using specific genetic markers of Type 1 diabetes and Type 2 diabetes susceptibility [45].

With regard to inferring causality, our inclusion only of those studies that measured BMI prior to diagnosis of Type 1 diabetes provides clear evidence for a temporal relationship between exposure and outcome. We also found evidence for a dose–dependent effect, based on results of BMI as a continuous variable. Overt demonstration of a causal relationship between childhood obesity and Type 1 diabetes from randomized controlled trials of obesity treatment or prevention would be infeasible because of the relative infrequency of Type 1 diabetes. However, it is possible that future surveillance of Type 1 diabetes could indicate whether trends in its incidence continue to reflect changes in the prevalence of childhood obesity.

Clinical relevance

Childhood obesity is a global problem. For the general population, prevention of childhood obesity is already an established public health goal. However, the identification of BMI as a potentially modifiable risk factor for Type 1 diabetes could provide even further support for the promotion of healthy lifestyles, particularly in populations with high incidence of Type 1 diabetes. There is evidence that weight gain very early in life is important in determining future risks of obesity [46] and Type 1 diabetes, and some studies have shown that nutritional counselling can be effective in influencing feeding behaviour in parents of young children [6].

It has been argued that increasing childhood obesity may simply lead to earlier presentation of Type 1 diabetes in those who are genetically susceptible, rather than increasing lifetime risk of disease [13–21]. The Belgian Diabetes Registry reported an increasing incidence of Type 1 diabetes before age 15 years between 1989 to 2000, which was balanced by a decreasing incidence between ages 15 and 40 years, and consequently there was no change in the overall age group of 0–39 years [47]. Unfortunately, seven of the nine studies that we identified had studied only childhood Type 1 diabetes as the outcome (Table 2). Both Lammi *et al.* [28] and Viner *et al.* [27] reported positive associations with childhood obesity and/or BMI and risk of Type 1 diabetes up to ages 39 and 30 years, respectively. However, even if the influence of childhood obesity were confined to an earlier age at onset, potentially delaying the onset of Type 1 diabetes could have substantial benefits as the risks of retinopathy, nephropathy, neuropathy and cardiovascular disease are related to the duration of diabetes [48,49].

Conclusion

Our systematic review indicates a likely association between childhood obesity, or higher BMI, and subsequent increased risk of childhood-onset Type 1 diabetes. It is unclear at what age BMI has the greatest impact nor the underlying mechanism; however, reduction in Type 1 diabetes should be considered as a potential additional benefit of preventing childhood obesity.

Competing interests

Nothing to declare.

References

1 Condon J, Shaw JE, Luciano M, Kyvik KO, Martin NG, Duffy DL. A study of diabetes mellitus within a large sample of Australian twins. *Twin Res Hum Genet* 2008; **11**: 28–40.
2 Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. Concordance for islet autoimmunity among monozygotic twins. *N Engl J Med* 2008; **359**: 2849–2850.
3 Kondrashova A, Reunanen A, Romanov A, Karvonen A, Viskari H, Vesikari T *et al.* "A six-fold gradient in the incidence of type 1 diabetes at the eastern border of Finland. *Ann Med* 2005; **37**: 67–71.
4 Green A, Patterson CC. Trends in the incidence of childhood-onset diabetes in Europe 1989–1998. *Diabetologia* 2001; **44**: B3–B8.
5 DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990–1999. *Diabet Med* 2006; **23**: 857–866.
6 Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. *Diabetologia* 2006; **49**: 20–24.
7 Baum JD, Ounsted M, Smith MA. Weight gain in infancy and subsequent development of diabetes mellitus in childhood. *Lancet* 1975; **360**: 866.
8 Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. *Obes Rev* 2004; **5**: S4–85.
9 OECD. *Health at a Glance 2009: OECD Indicators*. Paris: Organization for Economic Co-Operation and Development Press, 2009: 38–51.
10 Daneman D. Type 1 diabetes. *Lancet* 2006; **367**: 847–858.
11 Harder T, Roepke K, Diller N, Stechling Y, Dudenhausen JW, Plagemann A. Birth weight, early weight gain, and subsequent risk of Type 1 diabetes: systematic review and meta-analysis. *Am J Epidemiol* 2009; **169**: 1428–1436.
12 Gale EAM. Spring harvest? Reflections on the rise of type 1 diabetes. *Diabetologia* 2005; **48**: 2445–2450.
13 Kibirige M, Metcalf B, Renuka R, Wilkin TJ. Testing the Accelerator Hypothesis: the relationship between body mass and age at diagnosis of type 1 diabetes. *Diabetes Care* 2003; **26**: 2865–2870.
14 Knerr I, Wolf J, Reinehr T, Stachow R, Grabert M, Schober E *et al.* The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9248 German and Austrian children with type 1 diabetes mellitus. *Diabetologia* 2005; **48**: 2501–2504.
15 O'Connell MA, Donath S, Cameron FJ. Major increase in Type 1 diabetes—no support for the Accelerator Hypothesis. *Diabet Med* 2007; **24**: 920–923.
16 Evertsen J, Alemzadeh R, Wang X. Increasing incidence of pediatric Type 1 diabetes mellitus in southeastern Wisconsin: relationship with body weight at diagnosis. *PLoS One* 2009; **4**: e6873.

17 Gimenez M, Aguilera E, Castell C, De Lara N, Nicolau J, Conget I. Relationship between BMI and age at diagnosis of Type 1 diabetes in a Mediterranean area in the period of 1990–2004. *Diabetes Care* 2007; **30**: 1593–1595.
18 Kordonouri O, Hartmann R. Higher body weight is associated with earlier onset of Type 1 diabetes in children: confirming the 'Accelerator Hypothesis'. *Diabet Med* 2005; **22**: 1783–1784.
19 Porter JR. Braking the Accelerator Hypothesis? *Diabetologia* 2004; **47**: 352–356.
20 Dabelea D, D'Agostino RB, Mayer-Davis EJ, Pettitt DJ, Imperatore G, Dolan LM *et al*. Testing the Accelerator Hypothesis: Body size, β-cell function, and age at onset of type 1 (autoimmune) diabetes. *Diabetes Care* 2006; **29**: 290–294.
21 Betts P, Mulligan J, Ward P, Smith B, Wilkin T. Increasing body weight predicts the earlier onset of insulin-dependent diabetes in childhood: testing the 'accelerator hypothesis'(2). *Diabet Med* 2004; **22**: 144–151.
22 Harris RJ, Bradburn MJ, Deeks JJ, Harbord RM, Altman DG, Sterne JAC. metan: fixed- and random-effects meta-analysis. *Stata J* 2008; **8**: 3–28.
23 StataCorp. 2005. *Stata Statistical Software: Release 9*. College Station, TX: StataCorp LP.
24 Svensson J, Carstensen B, Mortensen HB, Borch-Johnsen K. Growth in the first year of life and the risk of type 1 diabetes in a Danish population. *Paediatr Perinat Epidemiol* 2007; **21**: 44–48.
25 EURODIAB Substudy 2 Study Group. Rapid early growth is associated with increased risk of childhood Type 1 diabetes in various European populations. *Diabetes Care* 2002; **25**: 1755–1760.
26 Hypponen E, Virtanen SM, Kenward MG, Knip M, Akerblom HK. Obesity, increased linear growth, and risk of Type 1 diabetes in children. *Diabetes Care* 2000; **23**: 1755–1760.
27 Viner RM, Hindmarsh PC, Taylor B, Cole TJ. Childhood body mass index (BMI), breastfeeding and risk of Type 1 diabetes: findings from a longitudinal national birth cohort. *Diabet Med* 2008; **25**: 1056–1061.
28 Lammi N, Moltchanova E, Blomstedt PA, Tuomilehto J, Eriksson JG, Karvonen M. Childhood BMI trajectories and the risk of developing young adult onset diabetes. *Diabetologia* 2009; **52**: 408–414.
29 Ljungkrantz M, Ludvigsson J, Samuelsson U. Type 1 diabetes: increased height and weight gains in early childhood. *Pediatr Diabetes* 2008; **9**: 50–56.
30 Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalised likelihood. *Stat Med* 1998; **17**: 404–429.
31 Bruining GJ. Association between infant growth before onset of juvenile type-1 diabetes and autoantibodies to IA-2. *Lancet* 2000; **356**: 655–656.
32 Pundziute-Lyckå A, Persson LA, Cedermark G, Jansson-Roth A, Nilsson U, Westin V *et al*. Diet, growth, and the risk for Type 1 diabetes in childhood. *Diabetes Care* 2004; **27**: 2784–2789.
33 Blom L, Persson LA, Dahlquist G. A high linear growth is associated with an increased risk of childhood diabetes mellitus. *Diabetologia* 1992; **35**: 528–533.
34 Lobstein T, Baur L, Uauy R. Appendix 1: reported prevalence of child and adolescent overweight and obesity. *Obes Rev* 2004; **5**: S86–97.
35 National Center for Health Statistics. *Growth Curves for Children Birth–18 Years*. Washington DC: National Center for Health Statistics, 1977.
36 Herngreen WP, van Buuren S, van Wieringen JC, Reerink JD, Verloove-Vanhorick SP, Ruys JH. Growth in length and weight from birth to 2 years of a representative sample of Netherlands children (born 1988–1989) related to socio-economic status and other background characteristics.' *Ann Hum Biol* 1994; **21**: 449–463.
37 Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E *et al*. Continuing positive secular growth change in the Netherlands 1995–1997. *Pediatr Res* 2000; **47**: 316–323.
38 Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *Br Med J* 2000; **320**: 1240–1243.
39 Sorva R, Tolppanen EM, Lankinen S, Perheentupa J. Growth evaluation: parent and child specific height standards. *Arch Dis Child* 1989; **64**: 1483–1487.
40 Karlberg P, Taranger J, Engström I, Karlberg J, Landström T, Lichtenstein H *et al*. Physical growth from birth to 16 years and longitudinal outcome of the study during the same age period. *Acta Paediatr Scand Suppl* 1976; **258**: 7–76.
41 Dibley MJ, Goldsby JB, Staehling NW, Trowbridge FL. Development of normalized curves for the international growth reference: historical and technical considerations. *Am J Clin Nutr* 1987; **46**: 736–748.
42 Nysom K, Molgaard C, Hutchings B, Michaelsen KF. Body mass index of 0 to 45-year-old Danes: reference values and comparison with published European reference values. *Int J Obes* 2001; **25**: 177–184.
43 Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. *Arch Dis Child* 1995; **73**: 25–29.
44 Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia* 2001; **44**: 914–922.
45 Raj SM, Howson JM, Walker NM, Cooper JD, Smyth DJ, Field SF *et al*. No association of multiple type 2 diabetes loci with type 1 diabetes. *Diabetologia* 2009; **52**: 2109–2116.
46 Ong K, Loos R. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr* 2006; **95**: 904–908.
47 Weets I, De Leeuw IH, Du Caju MV, Rooman R, Keymeulen B, Mathieu C *et al*. The incidence of type 1 diabetes in the age group 0–39 years has not increased in Antwerp (Belgium) between 1989 and 2000. *Diabetes Care* 2002; **25**: 840–846.
48 Donaghue KC, Chiarelli F, Trotta D, Allgrove J, Dahl-Jorgensen K. Microvascular and macrovascular complications associated with diabetes in children and adolescents. *Pediatr Diabetes* 2009; **10**: S195–203.
49 WHO. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*. Report of a WHO consultation. Geneva: Department of Non-Communicable Disease Surveillance, World Health Organisation, 1999.
50 IDF. *Diabetes Atlas*, 4th edition. Brussels: International Diabetes Federation, 2009.