Prenatal Growth, BMI, and Risk of Type 2 Diabetes by Early Midlife

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OBJECTIVE — Small size at birth has been associated with increased risk of type 2 diabetes. Our aim was to evaluate how risk of diabetes associated with low birth weight is affected by accumulation of body mass from childhood to adulthood.

RESEARCH DESIGN AND METHODS — Subjects from the 1958 British birth cohort (born 3–9 March 1958) have been followed regularly since birth. In the survey at 41 years of age, 88 participants reported type 2 diabetes (n = 10,683).

RESULTS — Participants in whom diabetes developed weighed less at birth and had higher BMIs than the others. Birth weight (adjusted for gestational age and sex) was inversely related to risk of diabetes (odds ratio for 1-SD change 0.76, 95% CI 0.56–0.99). All diabetic participants in the lowest third of birth weight were in the highest third of weight gain by 23 years of age. An increased risk of diabetes was found for those in the lowest third of BMI at 7 years of age (2.84, 1.2–6.9), but diabetic participants in this group had excessive weight gain to 23 years of age. All but one diabetic participant in the highest third of childhood BMI remained in the highest third until 23 years of age. Risk of diabetes by BMI at 23 years of age was 22.9-fold (95% CI 12–42) for obese participants and 3.8-fold (2.1–6.9) for overweight participants compared with those of normal weight.

CONCLUSIONS — There was no increase in risk of diabetes for small size at birth without excessive postnatal weight gain. Adult obesity was the most important risk factor for type 2 diabetes developing by early midlife.

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Obesity is the strongest known risk factor for type 2 diabetes, and excess risk is also observed for weight gain during adulthood (1–3). Small size at birth is associated with increased risk of type 2 diabetes, which has been suggested to be due to "programming" in the prenatal period (4). However, it has been argued that associations between birth weight and adult health outcomes may reflect subsequent growth trajectories (5). Low birth weight is often followed by accelerated postnatal growth, and this may be important for risk of diabetes in adult life. Childhood obesity was found to be more harmful for adult health than obesity developing later in some (6) but not all (7,8) studies. There is also evidence that thinness in childhood decreases insulin sensitivity later in life (9,10). Currently, there are few studies that simultaneously examine effects of prenatal growth and adiposity from childhood to adulthood on insulin sensitivity or the risk of type 2 diabetes.

The prevalence of type 2 diabetes is increasing worldwide (11), and it is becoming more common at younger ages (12). We evaluated the effect of birth weight and BMI on the risk of type 2 diabetes during 4 decades of follow-up of the 1958 British birth cohort. Our specific aim was to establish whether prenatal growth and childhood BMI increase the risk of type 2 diabetes through a child-to-adult trajectory of BMI that involves weight gain and development of adult obesity.

RESEARCH DESIGN AND METHODS

The sample subjects were all born 3–9 March 1958 in England, Scotland, and Wales (n = 16,751) (13), and follow-up was performed at ages 7, 11, 16, 23, 33, and 41 years (14,15). Birth data, including the child's weight and gestational age (as number of days from the first day of the last menstrual period), were collected by midwives in charge of the deliveries in 1958 and supplemented with information from obstetric records and interviews with the mother (13). Weights and heights were measured at 7, 11, 16, and 33 years of age and self-reported at 23 and 41 years of age (16). Adult height was determined at 33 years of age and complemented with values at 23 or 41 years of age. Prepregnancy weight for the each of the mothers of participants were self-reported and height was measured in 1958. Height and weight of both parents were reported in 1969.

In the 41-year survey, participants reporting that they had or had been told they had "non–insulin-dependent diabetes that is controlled by diet or tablets" were classified as diabetic. Age at diabetes onset was reported in years. North Thames MREC granted the ethical approval for the 41-year survey.

Numbers of participants

In the 1999–2000 survey, 87% (n = 14,288) of the eligible 16,460 cohort members were traced (17). From those traced, 859 refused to participate, 247 had died, and 394 had emigrated. Information on diabetes was obtained for 11,368 participants. Immigrants to the study were excluded due to the lack of birth data (n = 585). Participants reporting type 1 diabetes (n = 75) or another

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Anthropomethric characteristics by diabetes status*

	No diabetes at 41 years of age		Type 2 diabetes by 41 years of age		Difference in SD score (95% CI)
	n	Mean	*n*	Mean	
Birth weight (g)	10,257	3,338	85	3,248	−90 (−201 to 21)
Birth weight (SD score)*	9,290	0.08	75	−0.17	−0.25 (−0.47 to −0.03)
BMI					
Mother					
in 1957	10,299	22.9	84	23.8	0.26 (0.05–0.47)
in 1969	8,863	24.1	72	25.6	0.38 (0.09–0.65)
Father in 1969	8,620	24.7	67	25.8	0.38 (0.14–0.61)
Cohort member					
at 7 years†	8,728	15.9	70	16.1	0.48 (0.25–0.71)
at 11 years†	9,699	17.5	75	19.9	0.94 (0.72–1.17)
at 16 years†	9,616	20.4	75	24.0	1.31 (1.08–1.53)
at 23 years†	8,893	22.5	65	27.6	1.65 (1.41–1.89)
at 33 years†	9,031	25.1	53	32.1	1.57 (1.31–1.84)

*Birth weight standardized for gestational age and sex; †data for participants with diabetes presented only if measured before the reported age at onset.

type of diabetes ($n = 25$) were excluded, leaving 10,683 individuals for the analyses. The sample further depended on available data on birth weight and BMI. For diabetic participants, information on BMI was used only if measured before the age of diagnosis.

Statistical analysis

Standardized birth weight was determined as the deviation in SD score from the sex-specific mean birth weight for gestational age. BMI at 7, 11, 16, and 23 years of age was standardized separately for sex (BMI SD score). To reduce losses due to missing information, BMI (SD score) at 11 and 16 years of age were estimated for those with information both before and after the age using a linear function ($n =$ 1,361 and 2,175, respectively). Gain in weight was examined by comparing standardized measures (birth weight or BMI) at different time points. Rates of weight gain are presented as a 1-SD score increase over 5 years.

Because the number of diabetic participants was relatively small, analyses are presented for sexes combined. This was justified as both men and women with diabetes had higher BMIs than nondiabetic participants and a similar pattern of BMI increase with age. Prevalence of type 2 diabetes was compared across the thirds of birth weight (SD score) and BMI (SD score) at different ages and cross-classified by subsequent BMI (SD score) increase by 7, 11, 16, and/or 23 years of age. Random effects models were used to compare the difference in slopes for increase in BMI (SD score) between the affected and unaffected participants. Associations between birth weight or BMI and risk of diabetes were evaluated by univariate and multivariate logistic regression. Analyses were performed using the Stata software package (version 7; Stata, College Station, TX) (18).

RESULTS — By 41 years of age, the study sample included 88 cases of diabetes. Prevalence of diabetes was somewhat greater in men than in women (8.5 vs. 7.9 cases per 1,000, respectively). The median age at diagnosis was 38 years; diabetes was diagnosed in 7 patients before 23 years of age, in 14 patients between 23 and 32 years of age, and in 66 patients (75%) after 33 years of age. Age at diagnosis was unknown for one participant.

Birth weight and BMI before development of diabetes

Birth weight standardized for gestational age was lower in diabetic participants than in others, an effect that was greater than for crude birth weight (Table 1). The median length of gestation was 40.7 weeks for affected and 40.2 weeks for unaffected participants. From 7 years onward, diabetic participants had higher

Table 2—*Cumulative prevalence of type 2 diabetes by birth weight or BMI at different ages**

	Prevalence per 1,000 (diabetics/nondiabetics)	BMI at age 23 years of age	
		Lowest or middle third†	Upper third†
Birth weight			
Lowest third	9.2 (20/2,145)	2.7 (4)	23.6 (16)
Middle third	6.4 (14/2,180)	1.3 (2)	17.2 (12)
Upper third	5.4 (14/2,220)	2.8 (4)	12.4 (10)
BMI at age 7 years			
Lowest third	8.1 (21/2,421)	4.3 (9)	24.2 (12)
Middle third	2.9 (7/2,421)	1.2 (2)	6.9 (5)
Upper third	11.4 (28/2,435)	0.8 (1)	21.6 (27)
BMI at age 11 years			
Lowest third	5.7 (16/2,785)	3.7 (9)	20.4 (7)
Middle third	3.5 (10/2,818)	1.0 (2)	10.0 (8)
Upper third	12.5 (35/2,763)	0.9 (1)	20.6 (34)
BMI at age 16 years			
Lowest third	2.8 (8/2,883)	1.1 (3)	23.9 (5)
Middle third	3.4 (10/2,925)	2.3 (5)	6.7 (5)
Upper third	15.3 (44/2,829)	4.3 (4)	20.6 (40)

Data are *n* (%). *All categories based on standardized measures; birth weight standardized for gestational age and sex, BMI standardized for sex. Data restricted to participants with information from age under investigation and on BMI at 23 years of age. Data for participants with diabetes restricted to measurements obtained before the reported age at onset. †Number of diabetic subjects presented in parentheses. Sex-specific cutoff points for the 33rd and 66th centiles. Standardized birth weight −0.34, 0.45; BMI at 7 years: 15.3, 16.3; BMI at 11 years: 16.1, 17.6; BMI at 16 years: 19.0, 20.7; BMI at 23 years: 21.8, 23.8. Females: Standardized birth weight −0.37, 0.42; BMI at 7 years: 15.0, 16.3; BMI at 11 years: 16.2, 18.1; BMI at 16 years: 19.6, 21.7; BMI at 23 years: 20.4, 22.5.

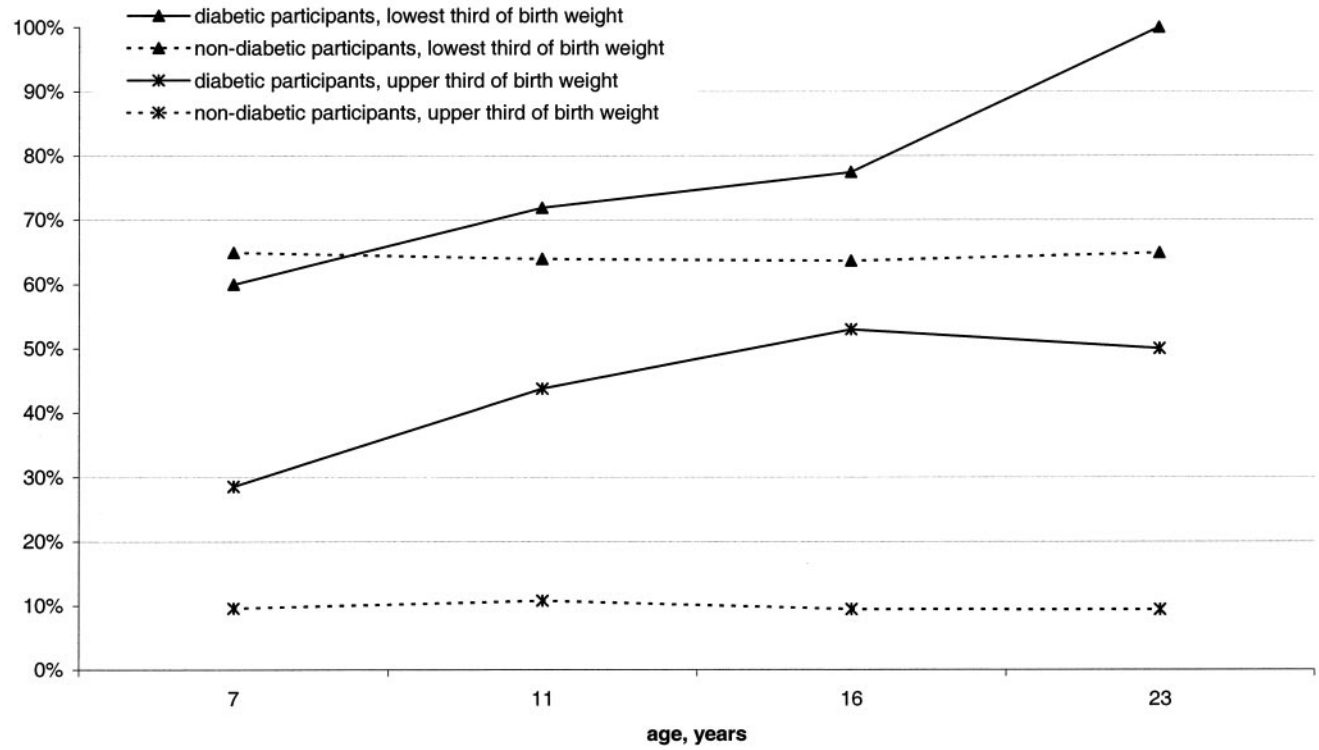

Figure 1—*Proportion in the highest one-third of BMI gain by thirds of birth weight.*

BMIs than others, and this difference became greater with age ($P < 0.001$) (Table 1).

Prevalence and risk of diabetes

Most diabetic participants were in the highest third of BMI at 23 years of age, and the prevalence of diabetes increased steeply with BMI (0.4, 3.5, and 17.2 per 1,000, from the lowest to highest thirds, respectively). There was some excess in the cumulative prevalence of diabetes in the lowest third of birth weight (Table 2). For all participants in whom diabetes developed, small size at birth was followed by excessive weight gain, as measured by being in the highest third of BMI gain by 23 years of age (Fig. 1). Prevalence of diabetes was elevated in both the lowest and highest third of BMI at 7 years of age, and these differences were most marked in the highest third of adult BMI (Table 2). Of the participants in the lowest third of BMI at 7 years of age, 81% of the affected and 54% of unaffected individuals were in the highest third of BMI gain by 23 years of age. Also, diabetic participants who were in the highest third of BMI at 7 years of age had a high rate of BMI increase (64% in the highest third by 23 years of age), whereas the same was true only for 17% of unaffected individuals. All but one diabetic participant in the highest third of BMI at 7 or 11 years of age remained in the highest third of BMI until 23 years of age.

We next tested the relationships between birth weight and BMI, allowing for adult obesity or BMI gain by 23 years of age (Table 3). There was no interaction between birth weight and BMI in relation to risk of diabetes at 23 years of age ($P = 0.78$). An inverse association between birth weight and risk of diabetes was little affected by adjusting for BMI at 23 years, whereas controlling for BMI gain from birth to 23 years of age reversed the direction of the estimate (Table 3). Similarly, the association between low childhood BMI and risk of diabetes was partly explained by allowing for differential weight gain to adulthood. As the participants grew older, the unadjusted U-shaped relationship between diabetes and BMI became linear and strongly positive for adult BMI. Using the World Health Organization (WHO) classification for obesity (BMI $\geq$30 kg/m^2) and overweight (BMI $\geq$25 but $<$30 kg/m^2), the risk of diabetes was 22.9-fold (95% CI 12–42) and 3.8-fold (2.1–6.9), respectively, compared with participants with normal weight (BMI $<$25 kg/m^2).

BMI gain and risk of diabetes

BMI gain during each interval was associated with risk of diabetes, and the estimates strengthened with age (Table 4). These associations remained after controlling for birth weight and BMI gain at other life stages, but a trend with age was not evident in these mutually adjusted models. Adjustment for BMI at 23 years of age eliminated the association between BMI gain and risk of diabetes, suggesting that adult BMI was on the causal pathway.

Parental BMI

Parents of diabetic participants had higher BMIs than parents of nondiabetic individuals (Table 1). The associations between the BMI of the mother and father with risk of diabetes held after adjustment for the cohort member's birth weight (adjusted odds ratio [OR] for 1-SD score change 1.35, 95% CI 1.1–1.6; OR 1.41, 95% CI 1.1–1.7; respectively) but not after adjustment for the cohort member's own BMI (OR 0.94 and 1.07, respectively). Adjusting for the BMI of the mother or father slightly strengthened the association between birth weight and diabetes, but this strengthening effect was not evident after controlling for the cohort member's own BMI (results not presented).

Table 3—*Risk of type 2 diabetes by thirds of birth weight and BMI

	Adjusted for sex	Adjusted for sex and BMI gain by 23 years	Adjusted for sex and BMI at 23 years
Birth weight			
Lowest third	1.71 (0.9–3.2)	0.41 (0.2–0.8)	2.03 (1.1–3.9)
Middle third	1.07 (0.5–2.0)	0.55 (0.3–1.1)	1.22 (0.6–2.5)
Upper third	reference	reference	reference
Per 1-SD increase	0.76 (0.6–0.99)	1.55 (1.1–2.1)	0.71 (0.5–0.9)
Test for trend	$P = 0.04$	$P = 0.005$	$P = 0.01$
BMI at age 7 years			
Lowest third	2.84 (1.2–6.9)	1.72 (0.7–4.1)	3.47 (1.5–8.2)
Middle third	reference	reference	reference
Upper third	3.97 (1.7–9.1)	5.18 (2.2–11.9)	1.97 (0.8–4.7)
Per 1-SD increase	1.44 (1.2–1.7)	2.03 (1.6–2.5)	0.90 (0.7–1.1)
Test for trend	$P < 0.001$	$P < 0.001$	$P = 0.37$
Test for curvature	$P = 0.26$	$P = 0.41$	$P = 0.41$
BMI at age 11 years			
Lowest third	1.73 (0.8–4.0)	1.64 (0.7–3.8)	2.85 (1.3–6.5)
Middle third	reference	reference	reference
Upper third	3.59 (1.7–7.5)	4.96 (2.3–10.6)	1.57 (0.7–3.3)
Per 1-SD increase	1.78 (1.5–2.1)	2.25 (1.9–2.7)	1.06 (0.8–1.3)
Test for trend	$P < 0.001$	$P < 0.001$	$P = 0.62$
Test for curvature	$P = 0.99$	$P = 0.85$	$P = 0.86$
BMI at age 16 years			
Lowest third	0.62 (0.2–1.7)	0.54 (0.2–1.5)	0.93 (0.3–2.6)
Middle third	reference	reference	reference
Upper third	4.18 (2.1–8.4)	4.53 (2.3–9.1)	1.65 (0.8–3.5)
Per 1-SD increase	2.04 (1.7–2.4)	2.34 (2.0–2.8)	1.21 (0.9–1.6)
Test for trend	$P < 0.001$	$P < 0.001$	$P = 0.16$
BMI at age 23 years			
Lowest third	0.10 (0.01–0.78)	—	—
Middle third	reference		
Upper third	4.45 (2.3–8.9)		
Per 1-SD increase	2.25 (1.9–2.6)		
Test for trend	$P < 0.001$		

Data are OR (95% CI). *Numbers of subjects same as in Table 2. Birth weight standardized for gestational age and sex, BMI standardized for sex.

CONCLUSIONS — To our knowledge, this is the first study of type 2 diabetes to include information on birth weight and BMI from early childhood together with data on adult and parental obesity. In this nationwide birth cohort, we confirmed the overwhelming effect of adult obesity on risk of diabetes. Importantly, we report how low birth weight in all participants who developed type 2 diabetes was followed by excessive BMI gain from birth and also how children who were relatively large at birth or during childhood continued to gain weight rapidly.

Birth weight

As in previous reports (4,19–21), we found an increased risk of type 2 diabetes among subjects with low birth weight. However, in our study, smaller size at birth was followed by a relatively high gain in weight in all participants in whom diabetes developed. Despite consistencies in the association between birth weight and risk of diabetes in western populations, the underlying mechanisms are not well understood. It is not clear why some individuals with low birth weight start on a fast growth trajectory that increases susceptibility to diabetes. Observations from the Dutch Hunger Winter study suggest that undernutrition during fetal life may contribute both to development of obesity (22) and risk of type 2 diabetes (23). Our observation for lower birth weights of diabetic participants despite higher BMIs of their mothers is consistent with a prenatal growth restraint and the programming hypothesis. There is growing evidence that genetic factors may affect the association between low birth weight and risk of diabetes (24,25), which may also contribute to the excessive weight gain in susceptible individuals.

Childhood BMI and rate of weight gain

Our findings agree with previous studies of type 2 diabetes and insulin resistance by showing an excess risk of diabetes for those who were relatively thin during childhood (10) and by showing high relative increases in BMI from an early age in participants in whom diabetes developed (19). Interestingly, half of participants with diabetes were already in the highest third of BMI at 7 years of age and they continued to gain weight rapidly. This agrees with a recent report on early age at

Table 4—*Risk of type 2 diabetes by rate of BMI gain* (per 1-SD score change in 5 years)*

	Adjusted for sex	Adjusted for sex, birth weight, and change at other intervals	Adjusted for sex and BMI at age 23 years
Increase from birth to 7 years	1.65 (1.3–2.2)	2.88 (2.1–4.0)	1.02 (0.8–1.4)
Test for trend	$P < 0.001$	$P < 0.001$	$P = 0.89$
Increase from 7 to 11 years	1.62 (1.3–1.9)	2.41 (1.9–3.1)	1.26 (1.0–1.6)
Test for trend	$P < 0.001$	$P < 0.001$	$P = 0.04$
Increase from 11 to 16 years	2.01 (1.5–2.8)	2.62 (1.8–3.8)	1.16 (0.8–1.6)
Test for trend	$P < 0.001$	$P < 0.001$	$P = 0.40$
Increase from 16 to 23 years	2.44 (1.7–3.5)	2.58 (1.8–3.7)	0.80 (0.6–1.1)
Test for trend	$P < 0.001$	$P < 0.001$	$P = 0.20$

Data are OR (95% CI). *BMI gain determined as the change in standardized measures between subsequent time points, birth weight standardized for gestational age and sex, BMI standardized for sex.

adiposity rebound in individuals developing diabetes (26). Furthermore, in our study, all but one diabetic participant in the highest third of childhood BMI remained in the highest third until adulthood, suggesting that diabetes did not develop in participants who were overweight in childhood but who subsequently maintained normal weight.

Methodological considerations

Some study limitations arise from following such a large population over a long period of time. Losses to follow-up are inevitable, but as described previously, for most purposes, this has not caused major bias (14,16). Inherent to all epidemiological studies on growth is the strong dependence between separate measures of size. There is no consensus on how such data should be analyzed, and we focused on individual growth pathways. In our study, a rapid postnatal weight gain was observed for most diabetic individuals. The magnitude of disproportionate BMI growth in participants in whom diabetes developed was also affecting the association between birth weight and risk of diabetes; after accounting for BMI gain, the inverse relation reversed direction. This can be explained by two distinct pathways characteristic for diabetic individuals but much less common for others: first, in all participants in whom diabetes developed, birth size was followed by rapid BMI gain, and second, diabetic participants who were relatively large at birth tended to continue with an excessive increase in size over time. It is not possible to discount increased risk of diabetes for small birth size without disproportionate BMI gain, even though this seems to be an uncommon pathway. Similarly for overweight children, it is difficult to assess their risks aside from their tendency to become fatter adults. Our simple analytical approach has the advantage of demonstrating the typical patterns of weight gain over the life course relevant for most diabetic individuals.

Our study was confined to type 2 diabetes with early onset (by 41 years of age); therefore, extrapolation to older ages must be done cautiously. Although obesity is an established risk factor for type 2 diabetes at all ages (12), the susceptibility genes may differ (27) and early-onset diabetes could be more strongly associated with obesity than with more slowly developing disease. In some participants, initial diagnosis with type 2 diabetes may be slowly progressing cases of type 1 diabetes or cases of maturity-onset diabetes. Although obesity has been associated with risk of type 1 diabetes (28), the effect is weaker than for type 2 diabetes. Maturity-onset diabetes is autosomal dominantly inherited and obesity is relatively rare in these patients (29). Because we focused on the effect of overweight and change in BMI, misclassification by diabetes type is likely to lead to dilution rather than exaggeration of effect estimates. Self-reported information on diabetes agrees well with information from other sources (30).

In conclusion, in our study adult obesity was by far the strongest risk factor for development of type 2 diabetes by early midlife. Small size at birth in diabetic individuals seems to be followed by a relatively high gain in BMI.

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