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ARTICLE

Life-course weight characteristics and the risk of gestational diabetes

E. H. Yeung · F. B. Hu · C. G. Solomon · L. Chen · G. M. Louis · E. Schisterman · W. C. Willett · C. Zhang

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Abstract
Aims/hypothesis We prospectively determined the risk of gestational diabetes mellitus in association with life-course weight characteristics and adult abdominal adiposity.
Methods We investigated the joint and independent impact of birthweight, childhood size by somatotypes, adolescent and adult BMI, and abdominal adiposity on gestational diabetes mellitus risk among the 21,647 women in the Nurses' Health Study II who reported a singleton pregnancy between 1989 and 2001. A total of 1,386 incident cases of gestational diabetes mellitus were reported. Relative risk was estimated by pooled logistic regression adjusting for age, prematurity, race, smoking status, parental history of diabetes, age of first birth, parity and physical activity.
Results Birthweight was inversely associated with gestational diabetes mellitus risk (p=0.02 for trend). Childhood somatotypes at ages 5 and 10 years were not associated with risk. U-shaped associations were found for BMI at age 18 years and somatotype at age 20 years. Weight gain between adolescence and adulthood, pre-gravid BMI and abdominal adiposity were positively associated with risk (p<0.01 for all trends). Multivariate adjusted RRs for gestational diabetes from lowest to highest quintile of WHR were 1.00, 1.50, 1.51, 2.03, 2.12 (p=0.0003 for trend). Lower birthweight (<7 lb) without adulthood overweight (BMI>25 kg/m^2) was associated with a 20% increased risk (95% CI 1.02–1.41). However, adulthood overweight alone was related to a 2.36 times greater risk (95% CI 2.12–3.77).
Conclusions/interpretation Although lower birthweight is an independent risk factor for gestational diabetes mellitus, weight gain since early adulthood, and overall and central obesity in adulthood were more strongly associated with elevated risk of the condition independently of other known risk factors.

Keywords Birthweight · Body mass index · Gestational diabetes mellitus · Life-course weight · Waist

Abbreviations
MET Metabolic equivalent
NHSII Nurses' Health Study II

E. H. Yeung (✉) · G. M. Louis · E. Schisterman · C. Zhang (✉)
Epidemiology Branch, Division of Epidemiology,
Statistics, and Prevention Research,
Eunice Kennedy Shriver National Institute of Child Health
and Human Development,
6100 Executive Blvd, 7B03,
Bethesda, MD 20892, USA
e-mail: yeungedw@mail.nih.gov
e-mail: zhangcu@mail.nih.gov

F. B. Hu · W. C. Willett
Departments of Nutrition and Epidemiology,
Harvard School of Public Health,
Boston, MA, USA

F. B. Hu · W. C. Willett
Channing Laboratory, Department of Medicine,
Brigham and Women's Hospital and Harvard Medical School,
Boston, MA, USA

C. G. Solomon
Divisions of General Medicine and Women's Health,
Department of Medicine,
Brigham and Women's Hospital and Harvard Medical School,
Boston, MA, USA

L. Chen
Epidemiology Program, School of Public Health,
Louisiana State University Health Science Center,
New Orleans, LA, USA

Introduction

Gestational diabetes mellitus is glucose intolerance with first recognition during pregnancy and stems from the failure to adapt to the increased metabolic demands of pregnancy [1]. The condition complicates approximately 7% of all pregnancies in the USA and is associated with substantially increased future risk of type 2 diabetes in the mothers. It also confers increased risk of obesity and other metabolic syndrome conditions on the offspring, which could last into adulthood [1].

Although pre-gravid obesity is a recognised risk factor for gestational diabetes mellitus, very few studies have comprehensively examined weight characteristics over the life-course. Low birthweight has been associated with an increased risk of gestational diabetes [2]. However, data assessing whether this association is independent of important confounders have been limited. Larger childhood body shape has been associated with lower levels of IGF-1 [3], which, in turn, is associated with decreased insulin secretion and increased risk of type 2 diabetes [4]. Data on the relationship between childhood adiposity and gestational diabetes mellitus risk are lacking. However, adolescent [5] and pre-gravid adulthood obesity [6] have been associated with gestational diabetes risk. In addition, although abdominal obesity is a strong risk factor for type 2 diabetes among non-pregnant individuals [7], its association with gestational diabetes risk has not been well studied.

Longitudinal changes in weight or crossing of weight categories has been suggested to be as or more important for development of insulin resistance and type 2 diabetes than measures of weight at one point in the life course [8]. In an earlier report from the Nurses' Health Study II [5], excessive weight gain from adolescence to adulthood was a strong risk factor of gestational diabetes [5]. However, only a few studies among pregnant or non-pregnant women have examined weight characteristics from birth to adulthood, and their findings on whether there are additional influences of their interactions on insulin resistance and glucose intolerance are conflicting [8–12]. Therefore, we investigated associations of life course weight and adult abdominal adiposity with the development of gestational diabetes mellitus in a prospective cohort of women from the Nurses' Health Study II (NHSII). [5]

Methods

Study population The NHSII is an ongoing prospective study, which originally recruited 116,608 US female nurses between the ages of 25 to 42 years in 1989. Follow-up is conducted using biennial questionnaires on lifestyle and health information. Among the cohort, 27,863 women reported a pregnancy lasting at least 6 months between 1989 and 2001. Of these, 21,647 remained after exclusion of: (1) women who reported a multiple gestation (i.e. twins) or a diagnosis of diabetes, cancer, cardiovascular disease or gestational diabetes at baseline, or diabetes prior to gestational diabetes; and (2) women for whom information on birthweight, childhood body shape, adolescent BMI, adult BMI or dates of diagnosis for diabetes, or death was not available. In 1993, 64% of the participants reported their waist and hip circumferences. For analysis of abdominal adiposity and gestational diabetes, only women (n=4,981) who reported a singleton pregnancy after 1993 and provided information on waist and hip circumferences were included. This study was approved by the Institutional Review Board of the Partners Health Care System (Boston, MA, USA). Implied informed consent was assumed by the return of a completed questionnaire from each participant.

Assessment of weight characteristics Figure 1 shows the time of data collection for the primary exposures of interest. At baseline, body fatness at ages 5, 10 and 20 years was assessed by asking participants to report their shape at each age using a nine-level set of figures called somatotypes, originally developed by Stunkard et al [13] (category 1 being leanest, category 9 heaviest). Recalled somatotypes such as the ones used in the present study have been validated in older (mean age 73 years) and younger (mean age 21 years) women by comparison with childhood records of weight, height and calculated BMI [14, 15]. Somatotypes at ages 5, 10 and 20 years correlated fairly well with records (r=0.60, 0.65 and 0.66, respectively) [14]. Weight at age 18 and adult height and weight were self-reported at baseline. BMI was

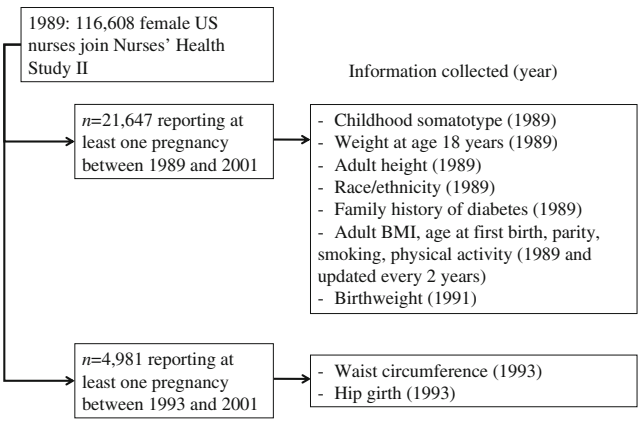

Fig. 1 Flow-chart of primary exposure data collected at baseline and follow-up in the NHSII. Prospective analysis of central adiposity measures included only women with a pregnancy after collection of these data in 1993 to end of follow-up in 2001 (n=4,981). Adult BMI, age at first birth, parity, smoking and physical activity were updated in biennial questions

calculated as weight (kg) divided by height (m) squared. Weight gain was the difference between baseline adult weight and weight at age 18 years.

In 1991, participants were asked to report their birthweight by five categories: <5.5, 5.5–6.9, 7.0–8.4, 8.5–9.9, or ≥10 lb (to convert values in lb to SI units (kg) multiply by 0.4536 kg). They were also asked whether they were born premature or of a multiple gestational birth. Due to the small number of gestational diabetes cases (n=12) among those in the ≥10 lb birthweight category, categories 8.5–9.9 and ≥10 lb were merged to form a ≥8.5 lb category. In a previous validation study involving 220 women, a strong correlation was found between self-reported birthweight and that recorded on birth certificates (Spearman's r=0.74) [16].

In 1993, waist and hip circumferences were reported to the nearest quarter inch in a subset of participants. In the NHSII, the correlation between recalled weight at age 18 and documented weight from college or nursing school records was 0.84 [5]. Correlations between self-report and technician conducted measurements were 0.96 for weight, 0.89 for waist circumference, 0.84 for hip circumference and 0.70 for WHR [5, 17].

Ascertainment of gestational diabetes mellitus Gestational diabetes mellitus was ascertained by self-report. A previous validation study of 114 women in NHSII showed that 94% of women reporting the condition had a physician diagnosis on record [18]. All women with confirmed diagnosis had abnormal glucose homeostasis and most physicians followed the National Diabetes Data Group diagnostic criteria. Moreover, among 100 women in NHSII who reported a pregnancy uncomplicated by gestational diabetes mellitus and were sent supplementary questionnaires to assess surveillance, 83% reported having a glucose loading test. This indicates a high degree of surveillance in this cohort [18].

Assessment of covariates Age was calculated as months from the reported birth date to date of questionnaire return. Race, smoking status, age of menarche, whether breastfed and family history of diabetes were reported at baseline in 1989. Parity and age at first birth were measured biennially. Alcohol consumption was reported on semi-quantitative food frequency questionnaires in years 1991 and 1995. Physical activity, in metabolic equivalent units (MET) derived from the average time spent in certain activities (e.g. jogging, running, cycling), was assessed in 1989, 1991 and 1997.

Statistical analysis Differences in baseline characteristics by birthweight categories were compared using χ^2 test for categorical variables and linear regression for continuous variables. Analyses of the main life-course weight characteristics (birthweight, childhood and adolescent weight characteristics, and BMI) were conducted within the full cohort of women who experienced a pregnancy between 1989 and 2001 (n=21,647). As central adiposity variables were collected in 1993, analyses for the association of these variables with gestational diabetes mellitus risk were conducted among women who experienced a pregnancy between 1993 and 2001 (n=4981).

Pooled logistic regression was used to estimate the relative risk of incident gestational diabetes mellitus for each weight characteristic, including: birthweight (<5.5, 5.5–6.9, 7.0–8.4, ≥8.5 lb); somatotype at ages 5, 10 and 20 years (1 to ≥5); BMI at age 18 years (<18, 18.0–19.9, 20.0–21.9, 22.0–24.9, 25–29.9, ≥30 kg/m^2); height (quintiles); adulthood BMI (<20, 20.0–21.9, 22.0–24.9, 25.0–29.9, ≥30 kg/m^2); and abdominal adiposity measures of waist circumference, WHR, hip girth and waist/height ratio (quintiles). Analyses were adjusted for age (five categories), race (white, black, other), smoking status (current, former, never), age at first birth (<24 years, ≥24 years), parity (number of pregnancies lasting >6 months), family history of diabetes (mother, father, both) and physical activity (quintiles of MET). Information on adult BMI, physical activity, parity and age at first birth was updated in subsequent questionnaires. These updated measures were used in adjusted analyses by including the most recent data for each 2-year follow-up interval. Thus if gestational diabetes mellitus was reported in 2001, BMI reported in 1999 was used. Analyses of birthweight were additionally adjusted for prematurity. To test for significant trends over the weight characteristic categories, linear models were fitted using the median values of each category of exposure (e.g. birthweight was tested using values of 5.00, 6.25, 7.75 and 9.75 lb).

We used 'centile crossing' methods as previously described [16] to analyse the joint effect between birthweight and adult BMI at baseline. Four centiles of BMI at baseline were created to correspond to the four centiles of birthweight (<7th, 7–37th, 37–86th and >86th percentile). For example, about 7% of the cohort reported a birthweight of <5.5 lb, so the first BMI centile category consisted of women who reported an adult BMI below the 7th centile based on the distribution of the cohort. The centiles of BMI were then cross-tabulated with birthweight categories to result in 16 categories for assessing joint effects. Adjusted relative risk estimates were determined using the reference group of women who had a normal birthweight (7.0–8.4 lb) and remained in the same centile of BMI (37–86th) as adults. An interaction term was created between centiles of BMI and birthweight categories to test for interaction.

We also investigated the joint effect of lower birthweight (<7.0 lb), adolescent overweight (BMI at age 18>25 kg/m^2) and adult overweight (BMI at baseline >25 kg/m^2) on gestational diabetes mellitus risk by creating an eight category variable with the reference being women who were 7 lb or heavier at birth, and lean in adolescence and adulthood.

In sensitivity analyses, we repeated the main analyses using incident cases of gestational diabetes mellitus and prevalent

cases at baseline; these analyses included women reporting a singleton birth prior to the start of the study. We also repeated analyses with only women born at full term, excluding prematurity. All analyses were conducted using SAS 8.2. (SAS Institute, Cary, NC, USA). All statistical tests were two-sided, with significance determined at $p<0.05$.

Results

At baseline, the mean age of the cohort was 30 years, 96% were white, 6.6% had low birthweight (<5.5 lb) and 14.6% had high birthweight (≥8.5 lb). Birthweight was positively associated with somatotypes at ages 5 to 20 years, and with adulthood weight and height (Table 1), whereas it was not significantly associated with BMI in adolescence ($p=0.09$) or adulthood ($p=0.38$), or with measures of abdominal adiposity ($p>0.15$). Maternal history of diabetes was more frequent among those with high birthweight, whereas paternal history was more frequent among those with low birthweight. Low birthweight was also associated with a slightly higher prevalence of current smoking.

Over the 12 years of follow-up, 1386 women developed incident gestational diabetes mellitus. Weight characteristics at different time points were significantly associated with the risk of gestational diabetes (Table 2). Women who

Table 1 Baseline characteristics for all participants, stratified by birthweight categories from the NHSII

Baseline characteristic (1989)[a]	Participant groups by birthweight category (lb)[b]				
	All	<5.5	5.5–6.9	7.0–8.4	≥8.5
Women (%)	100[a]	6.6	30.1	48.7	14.6
Age in 1989 (years)	30.4 (3)	30.7 (4)	30.3 (4)	30.4 (3)	30.2 (3)
White (%)	96.8	96.1	95.5	97.4	97.8
Premature birth (%)	8.2	56.9	10.9	2.2	0.9
Multiple gestation (%)	1.6	11.7	2.0	0.3	0.1
Breastfed (%)	32.1	18.1	30.2	34.6	34.1
Menarche at age 12 years (%)	30.1	30.2	28.9	30.6	30.4
Somatotype ≥5 at 5 years (%)	5.7	5.3	4.4	5.8	7.8
Somatotype ≥5 at 10 years (%)	10.2	10.3	9.3	10.1	12.5
Somatotype ≥5 at 20 years (%)	9.5	9.1	8.4	9.3	12.7
Nulliparous (%)	42.7	45.1	43.7	41.4	44.0
Age at first birth >24 years (%)	43.3	42.5	42.5	44.2	41.8
Maternal history of diabetes (%)	4.5	5.2	3.5	4.2	7.0
Paternal history of diabetes (%)	6.6	7.1	6.6	7.0	5.4
Both parents history of diabetes (%)	0.49	0.8	0.4	0.4	0.9
Active smoker (%)	9.3	10.9	9.4	9.1	9.3
Non-drinker (%)	39.8	39.3	40.3	39.4	40.0
Total activity (MET/week)	27.2 (40)	27.4 (40)	27.4 (40)	27.1 (40)	27.0 (40)
Weight (kg)	62.8 (12)	61.0 (12)	60.8 (11)	63.3 (12)	66.0 (12.7)
Height (m)	1.65 (0.07)	1.63 (0.07)	1.63 (0.06)	1.66 (0.06)	1.68 (0.06)
BMI at 18 years (kg/m^2)	21.0 (3)	20.9 (3)	20.8 (3)	23.1 (4)	21.4 (3.2)
Adult BMI (kg/m^2)	23.0 (4)	23.0 (4)	22.8 (4)	23.1 (4)	23.4 (4)
Weight gain (kg)	5.5 (8)	5.6 (9)	5.3 (8)	5.6 (9)	5.7 (9)
Waist circumference (cm)[c]	76 (11)	76 (11)	75 (10)	76 (11)	77 (11)
Hip circumference (cm)[c]	97 (10)	97 (11)	96 (9)	98 (10)	99 (10)
WHR[c]	0.78 (0.08)	0.78 (0.07)	0.78 (0.07)	0.78 (0.08)	0.78 (0.08)
Waist/height ratio[c]	0.46 (0.07)	0.47 (0.07)	0.46 (0.06)	0.46 (0.07)	0.46 (0.07)
Incident GDM (%)	6.4	7.1	7.2	6.1	5.5

All data presented as mean (SD) unless otherwise specified

[a] $n=21,647$

[b] To convert values in lb to SI units (kg) multiply by 0.4536 kg

[c] Among a subgroup of participants ($n=4,981$) who reported waist and hip measures in 1993 and had a singleton birth between 1993 and 2001

GDM, gestational diabetes mellitus

Table 2 Life-course weight characteristics and relative risk of gestational diabetes mellitus in NHSII

Characteristics	*n*	Cases (*n*)	Age-adjusted RR	*p* value	Multivariate RR[a]	*p* value
Birthweight (lb)[b]						
<5.5	1,425	101	1.07 (0.84–1.36)	0.60	0.97 (0.76–1.23)	0.77
5.5–6.9	6,519	468	1.17 (1.03–1.32)	0.01	1.12 (0.99–1.27)	0.06
7.0–8.4 (ref)	10,552	644	1.00	n/a	1.00	n/a
≥8.5	3,151	173	0.90 (0.76–1.06)	0.21	0.87 (0.73–1.03)	0.10
				0.005[c]		0.02[c]
Body shape at 5 years						
1	4,877	336	1.09 (0.95–1.25)	0.24	1.04 (0.91–1.20)	0.57
2 (ref)	7,629	486	1.00	n/a	1.00	n/a
3	5,320	306	0.90 (0.78–1.04)	0.15	0.91 (0.79–1.05)	0.18
4	2,596	170	1.03 (0.86–1.23)	0.75	1.00 (0.84–1.19)	1.00
≥5	1225	88	1.13 (0.90–1.42)	0.30	1.03 (0.82–1.30)	0.79
				0.66[c]		0.53[c]
Body shape at 10 years						
1	3,707	253	1.16 (1.00–1.36)	0.06	1.13 (0.97—1.32)	0.13
2 (ref)	7,308	432	1.00	n/a	1.00	n/a
3	5,132	324	1.07 (0.93–1.24)	0.37	1.09 (0.94–1.26)	0.26
4	3,292	206	1.06 (0.90–1.26)	0.48	1.04 (0.88–1.23)	0.64
≥5	2,208	171	1.32 (1.11–1.58)	0.002	1.19 (0.99–1.43)	0.06
				0.15[c]		0.49[c]
Body shape at 20 years						
1	658	55	1.41 (1.06–1.88)	0.02	1.33 (0.99–1.77)	0.06
2 (ref)	5,430	330	1.00	n/a	1.00	n/a
3	8,741	520	0.98 (0.85–1.12)	0.73	0.98 (0.85–1.12)	0.72
4	4,757	306	1.05 (0.90–1.23)	0.51	1.02 (0.87–1.20)	0.80
≥5	2,061	175	1.42 (1.18–1.70)	<0.001	1.25 (1.04–1.50)	0.02
				0.006[c]		0.12[c]
BMI (kg/m^2) at 18 years						
<18	2,015	144	1.32 (1.08–1.60)	0.006	1.23 (1.01–1.49)	0.04
18–<20 (ref)	6,945	382	1.00	n/a	1.00	n/a
20–<22	6,982	437	1.14 (0.99–1.31)	0.06	1.12 (0.97–1.29)	0.11
22–<25	3,991	249	1.13 (0.96–1.33)	0.13	1.07 (0.91–1.26)	0.43
25–<30	1,323	128	1.80 (1.47–2.21)	<0.001	1.55 (1.26–1.90)	<0.001
≥30	391	46	2.22 (1.63–3.03)	<0.001	1.74 (1.27–2.38)	0.001
				<0.001[c]		<0.001[c]
Adult BMI (kg/m^2)						
<20 (ref)	4,312	124	1.00	n/a	1.00	n/a
20–<22	6,516	232	1.11 (0.90–1.39)	0.33	1.12 (0.90–1.39)	0.32
22–<25	6,014	336	1.49 (1.21–1.83)	<0.001	1.49 (1.21–1.83)	<0.001
25–<30	3,422	378	2.50 (2.03–3.07)	<0.001	2.47 (2.01–3.04)	<0.001
≥30	1,383	316	4.37 (3.53–5.39)	<0.001	4.07 (3.28–5.05)	<0.001
				<0.001[c]		<0.001[c]
Weight change (kg)						
Loss of ≥5	1,178	52	0.95 (0.71–1.27)	0.73	0.86 (0.64–1.14)	0.29
±4.9 (ref)	11,035	510	1.00	n/a	1.00	n/a
Gain of 5–9.9	4,736	344	1.61 (1.40–1.85)	<0.001	1.63 (1.42–1.87)	<0.001
Gain of 10–19.9	3,461	320	2.09 (1.81–2.40)	<0.001	2.15 (1.86–2.48)	<0.001
Gain of ≥20	1,237	160	3.03 (2.53–3.63)	<0.001	3.05 (2.53–3.67)	<0.001
				<0.001[c]		<0.001[c]

Table 2 (continued)

Characteristics	*n*	Cases (*n*)	Age-adjusted RR	*p* value	Multivariate RR[a]	*p* value
Height (m)						
1st quintile <1.58	3,724	315	1.00	n/a	1.00	n/a
2nd quintile 1.58–<1.63	5,803	390	0.79 (0.68–0.91)	0.002	0.84 (0.72–0.98)	0.02
3rd quintile 1.63–<1.65	2,922	181	0.72 (0.60–0.87)	0.001	0.79 (0.66–0.95)	0.01
4th quintile 1.65–<1.70	5,559	309	0.64 (0.55–0.75)	<0.001	0.69 (0.59–0.81)	<0.001
5th quintile ≥1.70	3,624	190	0.61 (0.51–0.73)	<0.001	0.66 (0.55–0.80)	<0.001
				<0.001[c]		<0.001[c]

Values other than *p* and *n* values are RR (95% CI)

[a] Adjusted for age, race, smoking, maternal and paternal history of diabetes, age of first birth, parity and physical activity

[b] To convert values in lb to SI units (kg) multiply by 0.4536 kg; models additionally adjusted for prematurity

[c] For trend

n/a, not applicable; ref, reference category

reported low (<5.5 lb) or below-average (5.5–6.9 lb) birthweight were more likely to have gestational diabetes mellitus than women who reported normal birthweight (7.0–8.4 lb); the linear association remained significant ($p=0.02$) after adjusting for age, race, prematurity, parity, family history, physical activity and adult BMI. In addition, overweight at age 10 years (somatotype ≥5) was significantly related to gestational diabetes mellitus risk in age-adjusted analyses, although the association was marginally significant after adjusting for other factors. There were U-shaped associations in risks observed for both adolescent size by BMI at age 18 years and somatotype at age 20 years. The significant association with thinness did not persist after adjustment for weight gain in adulthood (RR 1.12; 95% CI 0.92–1.36 for BMI<18 kg/m^2 vs BMI 18–<20 at age 18), although the association with large body size remained significant (RR 1.91; 95% CI 1.37–2.65 for BMI ≥30 at age 18). Adult BMI and weight gain since adolescence were significantly and positively associated with gestational diabetes mellitus ($p<0.001$ for both linear trends). Gestational diabetes mellitus risk was increased significantly even among women within the normal BMI range (22–25 kg/m^2) compared with the very lean (<20 kg/m^2) (RR 1.49; 95% CI 1.21–1.83). Greater height was significantly associated with decreased risk of gestational diabetes mellitus ($p<0.001$ for trend).

Among women ($n=4,981$) who measured their waist and hip circumferences, pre-gravid waist circumference, WHR and waist/height ratio were all significantly and positively associated with gestational diabetes mellitus risk ($p<0.001$ for all linear trends) (Fig. 2). Although risks were attenuated after adjustment for continuous BMI, the associations remained statistically significant. For instance, the relative risks from lowest to highest quintile of WHR after adjusting for continuous BMI and confounders were 1.00, 1.50, 1.51, 2.03, 2.12 (95% CI 1.38–3.27) ($p<0.001$ for trend). In comparison to women belonging to the lowest quintile of waist/height ratio, those in the highest quintile had a 2.75 (95% CI 1.62–4.66) times greater risk of gestational diabetes. Hip circumference was not associated

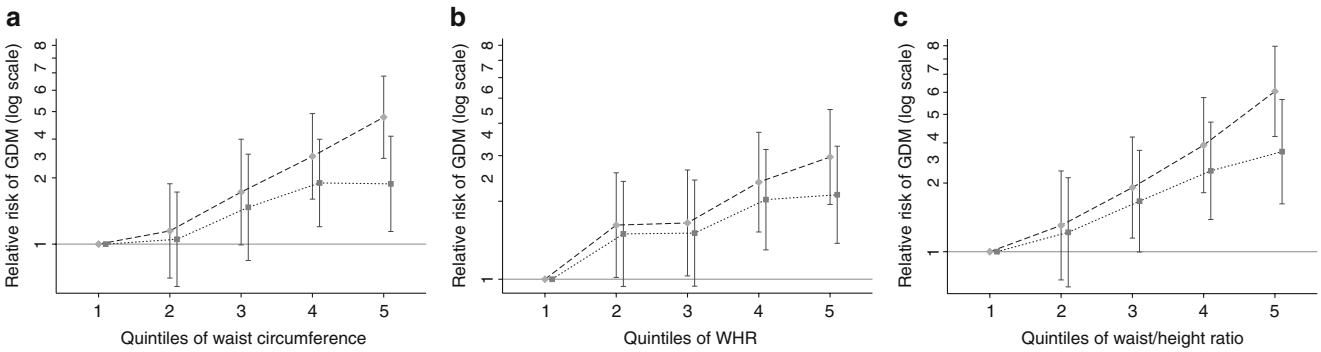

Fig. 2 Relative risks (95% CI) of gestational diabetes mellitus (GDM) by quintiles of waist (**a**), WHR (**b**) and waist/height ratio (**c**) ($n=4,981$). Dashed line, multivariate adjusted risks adjusted for age, race, smoking, maternal and paternal history of diabetes, age of first birth, parity and physical activity; dotted line, risks with addition of continuous BMI to the model above. All trends were significant ($p<0.005$)

with increased risk after adjusting for BMI. Since height has an inverse association with gestational diabetes mellitus, the waist/height ratio may be difficult to interpret. Sensitivity analyses were conducted with the residuals of waist adjusted for height. Associations using these residuals were slightly stronger than using waist alone, but less than with waist/height ratio, with the RR of the highest to lowest quintile comparison being 2.26 (95% CI 1.35–3.78).

We further investigated the independent and joint effects of birthweight and adult BMI on gestational diabetes risk (Table 3). The association between birthweight and risk did not differ by adult BMI. Even among women who were lean in adulthood (centile 7–37th), birthweight was inversely associated with gestational diabetes risk; the RR per birthweight category increase was 0.94 (95% CI 0.85–1.04). Similarly, regardless of birthweight category, each unit of BMI increase conferred a 7 to 9% increased risk (p= 0.37 for interaction).

To further understand the risk of gestational diabetes mellitus from cumulative exposure to overweight from adolescence to adulthood, combined with lower birthweight, we examined models with the addition of adolescent BMI. Women who reported all three conditions (i.e. birthweight <7 lb and overweight by BMI>25 at age 18 years and at adulthood) had a 2.83 times increased risk of gestational diabetes mellitus (95% CI 2.12–3.77) compared with those reporting none of these conditions (Fig. 3). Lower birthweight independently increased risk by 20% (95% CI 1.03–1.41). However, adult overweight had a much stronger effect, increasing risk by over twofold (RR 2.36; 2.00–2.79).

In sensitivity analyses, we explored whether the results differed when prevalent cases of gestational diabetes mellitus from baseline were included (n=3,939). Similar associations were observed for birthweight, although the magnitude of the associations increased slightly. Multivariate adjusted RR (95% CI) across birthweight groups, using 7.0 to 8.4 lb as reference and without combining the highest two categories, were 1.47 (1.33–1.62) for birthweight <5.5 lb, 1.18 (1.11–1.25) for 5.5–6.9 lb, 1.06 (1.01–1.10) for 8.5–9.9 lb and 1.06 (0.95–1.19) for ≥10 lb. (p<0.001 for trend). All results were similar in analyses among women who were born at full term (data not shown).

Discussion

In this large prospective cohort of women, lower birthweight, greater adolescent BMI and both greater adult BMI and abdominal adiposity were all significantly associated with an elevated risk of incident gestational diabetes mellitus; the elevation was independent of other known risk factors such as age, family history and physical activity. However, childhood adiposity alone (at ages 5 and 10 years) was not significantly associated with gestational diabetes mellitus. Lower birthweight combined with a high BMI in adolescence and adulthood was associated with a particularly increased risk.

United States birth data indicate high rates of low birthweight [19]. Almost one in twelve babies (8.2%) born in 2007 had a birthweight of less than 2,500 g (or 5.5 lb) [19]. Low birthweight has previously been linked with increased risk of metabolic dysfunction in child- and adulthood, the mechanism of which has been suggested to be fetal programming in response to maternal malnutrition [20]. In studies of malnutrition in youth, such as that occurring in famine conditions, low birthweight has been found to be associated with significant risks of cardiovascular disease and type 2 diabetes [21]. One hypothesised pathway by which this could occur is through epigenetic changes such as DNA methylation, which alter expression of growth or other metabolic factors in utero to compensate for nutritional insufficiencies, leading in later life to metabolic risk from exposure to over-nutrition [22]. This evidence has been primarily based on animal models, as it remains difficult to study in epidemiological settings [23]. Another possible mechanism is shared genetic risk factors of low birthweight and defects in insulin secretion [24]. Previous studies have generally shown either a linear inverse or a U-shaped association between gestational diabetes mellitus risk and birthweight [2]. Our ability to detect a U-shaped association may have been compromised by our inclusion in the highest birthweight category of all women reporting a birthweight of 8.5 lb or greater; this was done due to the relatively small number of cases with birthweight over 10 lb. In our sensitivity analysis including prevalent cases of gestational diabetes mellitus to increase sample size, we observed that birthweight over 10 lb was associated with increased risk of gestational diabetes mellitus in age-adjusted analysis. However, this association became statistically insignificant after controlling for other risk factors, suggesting that it is possible that the increase in gestational diabetes mellitus risk associated with higher birthweight in other studies could be attributable to uncontrolled confounders.

There were no significant associations between gestational diabetes mellitus and childhood somatotypes at ages 5 or 10 years, despite previous findings in this cohort that childhood somatotypes are associated with adult levels of insulin growth factors [3]. In other studies, childhood overweight has been associated with increased metabolic dysfunction, including hyperglycaemia during childhood and persisting into adulthood [25]. Our null finding may be due to misclassification resulting from use of recalled somatotypes as a measure of childhood adiposity, although the validity of this measure has been proven by comparison

Table 3 Combined effect of birthweight and adult adiposity on risk of gestational diabetes mellitus in the NHSII (n=21,647)

Adult BMI by centiles[d]	Mean BMI (kg/m^2)	Women (women with GDM[a]) (n) by birthweight category (lb)[c]				RR (95% CI)[b] by birthweight category (lb)[c]				RR (95% CI) per category birthweight
		<5.5	5.5–6.9	7.0–8.4	>8.5	<5.5	5.5–6.9	7.0–8.4	>8.5	
<7th	18	122 (9)	509 (27)	648 (24)	152 (5)	0.88 (0.45–1.74)	0.80 (0.53–1.17)	0.57 (0.37–0.86)	0.51 (0.21–1.23)	0.86 (0.69–1.09)
7th–37th	20	422 (19)	2,086 (115)	3,178 (129)	852 (35)	0.60 (0.37–0.98)	0.83 (0.67–1.03)	0.65 (0.53–0.79)	0.65 (0.45–0.92)	0.94 (0.85–1.04)
37th–86th	23	663 (44)	3,053 (214)	5,164 (319)	1,614 (79)	0.87 (0.62–1.23)	1.07 (0.89–1.27)	1.00[e]	0.76 (0.60–0.98)	0.94 (0.88–1.00)
>86th	31	218 (29)	871 (112)	1,562 (172)	533 (54)	1.75 (1.16–2.64)	1.99 (1.60–2.48)	1.77 (1.47–2.14)	1.52 (1.13–2.04)	0.94 (0.86–1.02)
RR per unit BMI						1.07 (1.03–1.11)	1.08 (1.06–1.10)	1.09 (1.07–1.10)	1.07 (1.04–1.10)	

[a] GDM, gestational diabetes

[b] Adjusted for age, race, prematurity, smoking, maternal and paternal history of type 2 diabetes, age of first birth, parity and physical activity

[c] To convert values in lb to SI units (kg) multiply by 0.4536 kg

[d] Calculated using self-reported BMI at baseline in 1989 and corresponding to the percentiles of birthweight by each category (to the nearest whole per cent)

[e] Reference category

Test for interaction between BMI and birthweight by cross-product was non-significant (p=0.37)

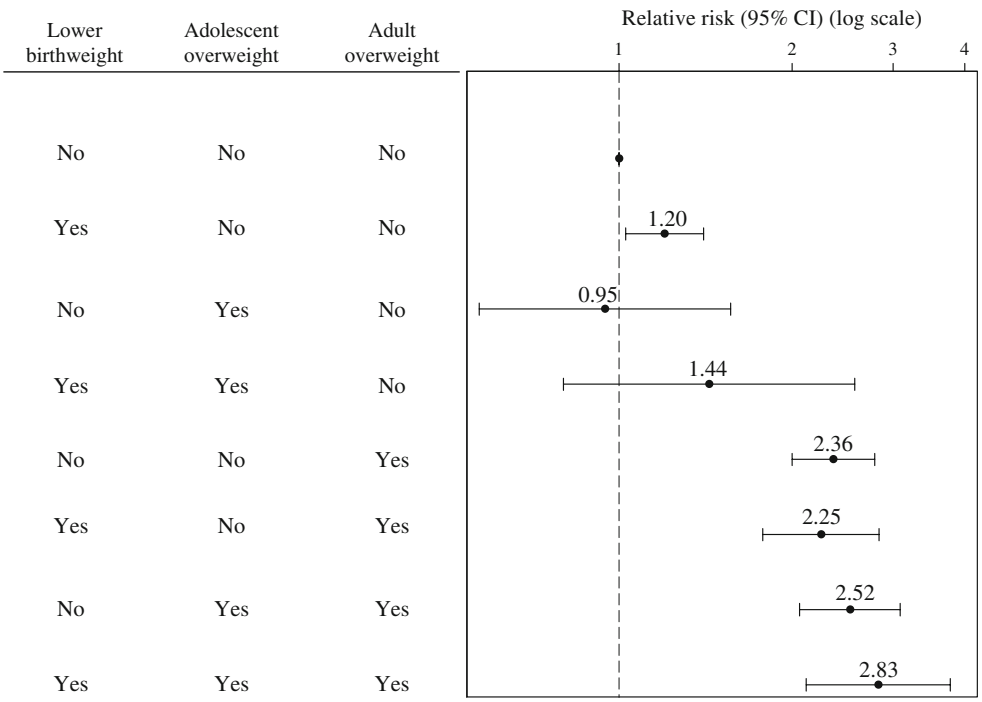

Fig. 3 Women were stratified by lower birthweight (<7.0 lb or 3.18 kg), adolescent overweight (BMI>25 kg/m^2 at age 18 years) and adult overweight (BMI>25 kg/m^2 at baseline). The reference category for the associations consisted of women who did not report any of these conditions. The adjusted relative risks (95% CI) of gestational diabetes mellitus among women reporting each of these exposures independently and in combination are shown

with childhood records of size [14, 15]. Another possible explanation could be that the women who had low birthweight or were premature had caught up by 5 or 10 years of age. Studies in type 2 diabetes have demonstrated that early age of adiposity rebound is an independent determinant of metabolic risk [26]. Our reports of childhood size did not capture this aspect of growth and it remains to be explored in future studies.

On the other hand, we found a U-shaped relationship between gestational diabetes mellitus risk and somatotypes at age 20 years, which was similar to results using BMI at age 18 years. The increased gestational diabetes mellitus risk observed by us in underweight individuals appeared to be explained by the greater subsequent weight gain in women who were leaner at age 18. The increased risk of gestational diabetes mellitus associated with adolescent overweight (BMI>25 kg/m^2) is in agreement with findings from studies of adolescent overweight, insulin resistance and type 2 diabetes [5].

Previous reports, including this cohort [5], have indicated that increased risk of gestational diabetes mellitus is associated with increased pre-gravid BMI, with risk in overweight women twice that in normal-weight women and with risk in morbidly obese women increased five- to sixfold [6]. Adult overweight was the strongest risk factor for gestational diabetes mellitus, with lower birthweight and adolescent overweight having minor effects when the three risk factors were assessed in combination. It is not surprising that adult overweight had stronger associations than early life risk factors, as it is more proximal to events and may already represent an underlying metabolic dysregulation. Our finding of increased gestational diabetes mellitus risk even among women with BMI 22 to 25 kg/m^2, as compared with leaner women, indicates that even BMIs in the 'normal' range may confer increased risk in pregnancy.

Added information on abdominal obesity, rather than reliance on BMI alone, could be one way to identify women at risk in the lower BMI categories. Prior studies of the association between central adiposity and incident gestational diabetes mellitus risk are scarce and have been limited by their cross-sectional design and/or small number of gestational diabetes mellitus cases [27, 28]. Our report is among the largest studies on abdominal adiposity and gestational diabetes mellitus risk. Consistent with findings from the present study, a cross-sectional study of pregnant women in Brazil (n=1,113) demonstrated significant and positive associations between glucose levels from OGTT and both waist circumference and WHR [27]. Our findings are also consistent with evidence from the prospective Coronary Artery Risk Development in Young Adults study, which demonstrated that increased pre-pregnancy waist and hip circumference, and WHR were significantly associated with increased risk of gestational diabetes mellitus [28]. We additionally looked at waist/height ratio and found stronger protective effects, possibly due to taller height being inversely associated with gestational diabetes mellitus as demonstrated here and as previously reported [29]. Our results, together with these findings, support the notion that visceral adiposity contributes to gestational diabetes mellitus risk beyond the risk associated with increased total body adiposity.

We found that lower birthweight was associated with increased gestational diabetes mellitus risk across a wide range of BMI values in adulthood. In contrast, a previous study using birth certificates reported that low birthweight was associated with increased gestational diabetes risk only among women with BMI less than 25 kg/m^2 [10]. Our finding of no qualitative interaction between adult BMI and birthweight in association with gestational diabetes mellitus risk is consistent with findings in studies of type 2 diabetes [8] and insulin resistance [12].

There were limitations to our study. Recall of weight characteristics is subject to misclassification, but previous validation studies have supported consistency with medical records or clinical measures [5, 17]. Misclassification may have led to underestimates of the true associations, but the prospective study design avoids bias in reporting related to subsequent disease status. We did not have information on gestational age or on other measures such as ponderal index at birth, which might provide more accurate measures of fetal growth and assessment of intrauterine growth restriction. Because of the observational nature of our study, we cannot prove the causality of the observed association or rule out the impact of residual confounding, although we controlled for most known risk factors of gestational diabetes. Birthweight information was not available for 14% of the eligible women; however, distributions of major characteristics (e.g. age, BMI, incidence of gestational diabetes mellitus etc.) were similar among individuals without birthweight information compared with those who reported it. We also acknowledge that we use the term 'pregravid' for any measures prior to pregnancy, despite variations in the length of time when data may have been collected prior to pregnancy. For BMI, which was updated every 2 years, the interval of time was short, but this was not the case for waist or hip measurements, with a median of 3 years elapsing before index pregnancy. However, it remains a strength to have information prior to pregnancy. The last limitation is that gestational diabetes mellitus was ascertained by self-report, which is dependent upon screening. Where universal screening was not practised, any misclassification of case status may not have been random, as obesity is a recognised indicator for screening. However, previous validation of this measure in this cohort suggests that the large majority of participants underwent glucose screening during their pregnancy [18]. The validation study also indicated a high degree of accuracy of self-reported gestational diabetes mellitus compared with medical record review [25].

The strengths of our report include the large sample size, which allowed us to explore interactions and provide precise estimates of gestational diabetes mellitus risk. In addition, NHSII collected detailed information, spanning participants' life course, on important risk factors such as parental diabetes history, physical activity and anthropometry.

In conclusion, lower birthweight, increased adiposity in adolescence and greater overall body and abdominal adiposity in adulthood were all significantly associated with an elevated risk of incident gestational diabetes mellitus; this elevation was independent of other known risk factors. Women who were born smaller than the average and who subsequently became overweight in adolescence and adulthood had the highest risk of gestational diabetes mellitus, whereas women born small, but who remained lean, only had a slightly increased risk. The finding that low birthweight and adult overweight are independently associated with gestational diabetes mellitus risk suggests that they may operate through different pathways. From a public health standpoint, however, overweight and obesity are associated with much greater absolute risks of gestational diabetes mellitus than low birthweight. Therefore, weight loss prior to pregnancy remains the most important strategy for women to prevent gestational diabetes mellitus.

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