Prenatal Exposures and Glucose Metabolism in Adulthood

Are effects mediated through birth weight and adiposity?

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OBJECTIVE — Birth weight has been associated with the risk of type 2 diabetes in several studies. We investigated whether prenatal influences on birth weight (gestational age, parity, preeclampsia, prepregnancy BMI, smoking during pregnancy, and socioeconomic position [SEP]) were associated with glucose metabolism in midlife and the role of birth weight for gestational age (BGA) and adult adiposity in mediating these associations.

RESEARCH DESIGN AND METHODS — Data from 7,518 participants of the 1958 British Birth Cohort with information on A1C at age 45 years were analyzed. Associations between prenatal exposures and A1C ≥6% were examined using a series of logistic regression models. The basic model consisted of all prenatal factors (except parity) adjusted for sex and family history of type 2 diabetes. Further adjustments included BGA only, concurrent adiposity only (BMI and waist circumference), and BGA plus adiposity.

RESULTS — In the basic model, preeclampsia (odds ratio 1.78 [95% CI 1.14–2.80]), prepregnancy BMI ≥25 kg/m^2 (1.90 [1.45–2.47]), maternal smoking (1.33 [1.04–1.71]), and manual SEP (1.87 [1.36–2.58]) were independently associated with A1C at 45 years of age. Adjustment for BGA had little impact on the prenatal factors/A1C associations, whereas adjustment for adult adiposity at 45 years substantially reduced associations for prepregnancy BMI, smoking during pregnancy, and SEP.

CONCLUSIONS — Prenatal exposures were related to blood glucose levels in mid-adulthood. Associations for several prenatal factors were largely mediated through adult adiposity but surprisingly not through birth weight. Prenatal exposures are likely to have the strongest effect on glucose metabolism indirectly through their influence on adiposity.

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An inverse relationship between birth weight (as a proxy for reduced fetal growth) and measures of glucose metabolism in adulthood, including the prevalence of type 2 diabetes, has been reported in several studies (1). According to the thrifty phenotype hypothesis, the association between reduced fetal growth and glucose metabolism in adulthood is related to poor fetal nutrition resulting from an adverse intrauterine environment (2). However, the effects of prenatal exposures on glucose metabolism in the offspring in later life are not clear. Studies have found a relationship between prenatal factors and offspring adiposity; for example, smoking during pregnancy or maternal overweight are associated with offspring obesity in adolescence (3,4). Furthermore, there may be a direct effect of smoking on obesity rather than operating indirectly through socioeconomic and lifestyle pathways in childhood (5).

Given the influence of prenatal exposures on established risk factors for glucose metabolism (birth weight and adiposity), it is plausible that these factors either directly or indirectly affect diabetes risk in adult life. Possible pathways and factors involved are represented schematically in Fig. 1. Birth weight (Fig. 1*A*) and adiposity (Fig. 1*B*) are associated with impaired glucose metabolism. In particular, those born small for gestational age who become obese as adults are at high risk of developing type 2 diabetes; however, increased birth weight is associated with increased adiposity and hence poor glucose control (Fig. 1*C*). Prenatal factors may directly affect glucose control (Fig. 1*D*) or be mediated through their effects on birth weight (Fig. 1*A* and *E*), adiposity (Fig. 1*B* and *G*), or both (Fig. 1*E* and *F*). Socioeconomic position (SEP) before and during pregnancy may be associated with glucose metabolism in adulthood through its effects on prenatal factors in addition to birth weight and adiposity. The plausibility of these associations over an individual's life course is supported by studies of blood pressure showing an association for maternal smoking and blood pressure during the prenatal period with blood pressure in offspring in childhood and adolescence (6). A few studies have reported that maternal obesity (7), gestational diabetes (7–9), and smoking during pregnancy (10) increase the risk of type 2 diabetes in offspring. Two recent studies have demonstrated relationships for preterm birth and glucose metabolism in childhood and adulthood independent of birth weight (11,12). However, evidence supporting independent effects for prenatal exposures and glucose metabolism in adulthood is scarce. We hypothesize that, as illustrated in Fig. 1, prenatal exposures will influence glucose metabolism and that their effects will be mediated through birth weight and/or adiposity during the life course. We investigate this hypothesis using data on key prenatal influences, including birth weight, adult adiposity, and

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Abbreviations: BGA, birth weight for gestational age; PMS, Perinatal Mortality Survey; SEP, socioeconomic position.

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

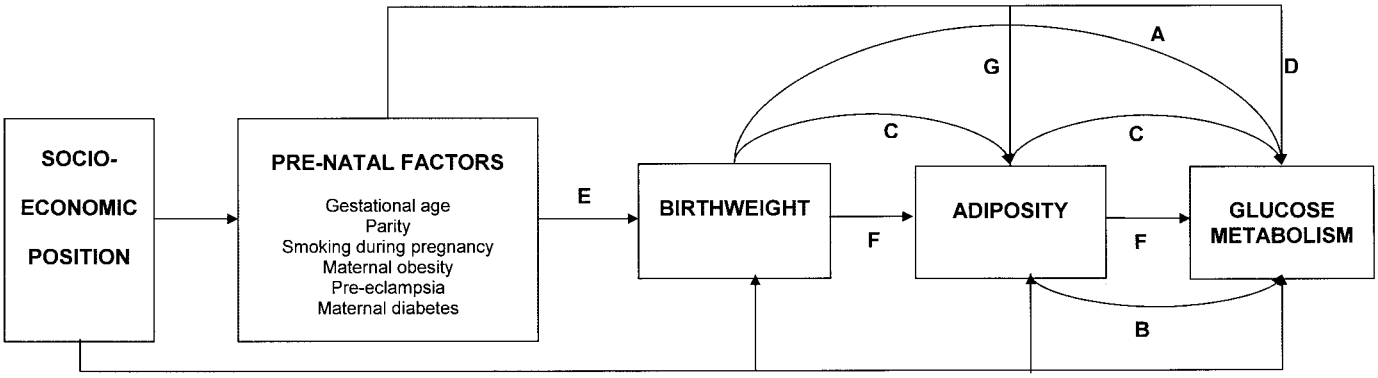

Figure 1— *Hypothesized relationships between early life environment, birth weight, adiposity, and glucose metabolism in adulthood. SEP before and during pregnancy may influence glucose metabolism through its effects on prenatal factors and/or through effects on birth weight and adiposity.* A*: Low birth weight is associated with poor glucose control.* B*: Increased adiposity is associated with poor glucose control.* C*: Increased birth weight is associated with increased adiposity and hence poor glucose control.* D*: Direct effect of prenatal factors on glucose control.* A *and* E*: Effect of prenatal factors on glucose control mediated through birth weight.* B *and* G*: Effect of prenatal factors on glucose control mediated through adiposity.* E *and* F*: Effect of prenatal factors on glucose control mediated through both birth weight and adiposity.*

glucose metabolism, in the 1958 British Birth Cohort.

RESEARCH DESIGN AND METHODS

— The 1958 British Birth Cohort consists of data on 17,638 participants originally enrolled in the Perinatal Mortality Survey (PMS) all born during 1 week in March 1958 in England, Scotland, and Wales who have been interviewed at intervals in childhood and adulthood (13). A further 920 immigrants with the same birth dates up to age 16 years were recruited for the study. A target sample of 12,069 cohort members were invited to participate in a biomedical survey at age 45 years; 9,377 (78%) individuals responded. We excluded 56 individuals with type 1 diabetes and 302 immigrants who had not been included in the PMS, since their perinatal data could not be obtained. The South East Multi-Centre Research Ethics Committee gave ethical approval for the biomedical survey.

Measures

Outcome. A1C at 45 years was measured from nonfasting venous blood samples using ion exchange high-performance liquid chromatography (Tosoh A1c2.2 Glycohemoglobin Analyser, HLC-723GHb; Tosoh, Tokyo, Japan) (14) at the Department of Clinical Biochemistry, Newcastle upon Tyne Hospitals NHS Foundation Trust. Results were standardized to the A1C assay used in the Diabetes Control and Complications Trial (15,16). The primary outcome used was A1C categorized as a binary variable using a cutoff of 6% (17,18). Given that treatment for diabetes will lower A1C, those with type 2 diabetes were assumed to have A1C ≥6% in this study. Individuals diagnosed with type 2 diabetes were identified from information collected at age 42 years. Participants reported whether a doctor had told them that they had "non–insulin-dependent diabetes that is controlled by diet or tablets". At age 45 the participants completed a survey in which the nurse collected information on currently prescribed medication (through direct observation of packaging) from which oral antidiabetes drugs were identified.

Early life exposures. Several prenatal factors were identified from the literature that have been shown to be associated with either birth weight, obesity in later life, cardiovascular disease, or type 2 diabetes including gestational age, parity, maternal body size, smoking during pregnancy, preeclampsia, gestational diabetes, and SEP. We modeled SEP as a prenatal factor because of its association with prenatal conditions and with adiposity and glucose metabolism in later life. The midwife collected data during the PMS on early life exposures at the birth of the child. Gestational age was classified as <38, 38–42, and >42 weeks. Parity was defined as previous pregnancies that had reached 28 weeks of gestation; categories were 0, 1, 2–3, and ≥4 pregnancies. Mothers' measured height was converted from inches to centimeters, and self-reported prepregnancy weight was converted from stones to kilograms. BMI was calculated as weight in kilograms divided by the square of height in meters and categorized as <18.5, 18.5–24.99, 25.00–29.99, and ≥30 kg/m^2. Information on maternal smoking was based on smoking after the 4th month of pregnancy because, at the time, smoking was thought to exert the greatest effect on birth weight in the later stages of pregnancy (19). Smoking was categorized as never smoked (not before or after 4th month of pregnancy), ex-smokers (smoked before but not after), light (1–9/day after the 4th month), medium (10–19/day) and heavy (≥20/day). Those who changed their smoking habits were classified as "variable" smokers. Preeclampsia was defined as albuminurea (not attributable to urinary tract infection) and diastolic blood pressure >90 mmHg (19). Of those with data at age 45 years, only three had mothers with gestational diabetes; hence, this factor was not considered further. SEP was based on the Registrar General's classification of the fathers' occupation at birth and grouped as I and II (professional and managerial), III nonmanual (unskilled), III manual (skilled), and IV and V (semi-skilled and unskilled manual). Single mother households were classified as IV and V. Where data were missing, father's SEP was used when the child was 7 years old.

Potential mediating factors. Birth weight was measured in pounds and ounces and converted into grams. For use in statistical modeling, birth weight was standardized for sex and gestational age (birth weight for gestational age [BGA]) and expressed as *Z* score tertiles. A nurse using standardized protocol and equipment (scales and stadiometer) measured height and weight of cohort members at 45 years of age without shoes and in light clothing. BMI was calculated as previ-

ously described. Waist circumference (centimeters) was measured midway between the costal margin and iliac crest.

Other confounding factors. To control for genetic predisposition to type 2 diabetes, we used information on whether first-degree relatives (parent or sibling) had diabetes, as obtained from two data sources. First, during a follow-up at age 7 years, parents of the cohort members were asked, "Is there a history of any diabetes in parents, brothers, or sisters?" Second, information on parental mortality from diabetes-related causes (original or underlying) was available until the end of December 2003 and coded according to the ICD-10 codes E10 to E14 (20).

Statistical analysis

Analyses were conducted using STATA version 9.2. Univariate relationships between prenatal factors, birth weight, BMI, and A1C were first explored; linear trends in the prevalence of A1C ≥6% and type 2 diabetes across categories of prenatal exposures were assessed using χ^2 trend tests, and variation in continuous measures (birth weight, BMI, and A1C) were tested by entering each prenatal variable as a continuous variable into regression models. A1C was log transformed and geometric means presented; robust estimation was used in regression models of A1C because the homoscedasticity assumption could not be met through transformation (21).

The role of BGA and adiposity as mediators of prenatal factor A1C associations was investigated using a series of logistic regression models. A basic model was fitted consisting of all prenatal variables simultaneously that were significantly associated with the main outcome (A1C ≥6% and/or type 2 diabetes) in univariate analyses, controlling for sex and family history of type 2 diabetes. A series of models was subsequently fitted with adjustments for BGA, adiposity at 45 years of age (BMI and waist circumference separately and together), and BGA and adiposity. Quadratic as well as linear terms for the mediators were tested because BMI and waist circumference had curvilinear associations with A1C, and collinearity was tested using the variance inflation factor. Prenatal exposures were modeled as dichotomous variables because the number with A1C ≥6% and/or type 2 diabetes was small in several of the exposure categories. Sex interactions were investigated for associations of prenatal exposures with the outcome using the likelihood ratio statistic that tests the assumption of no interaction by comparing the log likelihoods from two regression models, one without and one with the interaction term. No interactions were found, and results are presented for men and women combined.

Supplementary analyses were undertaken using two further outcomes, diagnosed type 2 diabetes and A1C ≥7%, since they are associated with type 2 diabetes diagnosed by the oral glucose tolerance test (22). The results for the three outcomes were generally consistent; hence, results for only one outcome (A1C ≥6% and/or type 2 diabetes) are presented here.

Missing data

Data at 45 years of age were available on A1C, BMI, and waist circumference for 7,518 individuals. The sample was broadly similar to the original birth population; for SEP at birth, 19.0% of the analysis sample compared with 17.2% of the original population was in classes I and II and 22.2% compared with 24.5%, respectively, in classes IV and V. There was also a modest underrepresentation at 45 years of age of those with a higher BMI at 33 years of age; BMI in the sample with data at 45 years of age was 0.5 kg/m^2 lower than in the sample without data. A total of 5,673 of 7,518 participants had complete data on prenatal factors and BGA. Those with A1C ≥6% and/or type 2 diabetes had more missing data than those with A1C <6% (32 vs. 24.7%; χ^2 = 9.4, P = 0.002). We therefore imputed the missing covariates using the "mice" method (multiple imputation by chained equations) described by Van Buuren et al. (23). As recommended, 10 copies of the original dataset imputed for missing data were created, and a regression analysis combining the results from each dataset was undertaken (24). Results based on a complete-case analysis were generally similar and therefore not reported. Information has been included where the results differ for statistical significance.

RESULTS

Table 1 describes the univariate relationships for prenatal factors with birth weight, BMI, and glucose metabolism at 45 years of age. The geometric mean A1C was 5.20% (95% CI 5.19–5.21%) and was higher for men (5.26 [5.24–5.27]) than women (5.14 [5.13–5.16]). The prevalence with A1C ≥6% was 2.61%; for type 2 diabetes, it was 1.32%. Increasing gestational age, parity, and prepregnancy BMI were associated with higher birth weight, whereas preeclampsia, smoking during pregnancy, and lower SEP were associated with lower birth weight. Similar trends were seen for BGA (data not shown). All factors except gestational age and parity were significantly associated with increased BMI in adulthood. A trend for increasing prevalence of A1C ≥6% (excluding type 2 diabetes) was found for lower gestational age, preeclampsia, higher prepregnancy BMI, and lower SEP. Results were similar for type 2 diabetes with the exception of trends for gestational age and preeclampsia, which were not statistically significant. An increased prevalence for either A1C ≥6% or type 2 diabetes existed for smoking during pregnancy but was only statistically significant for the two outcomes combined. The combined outcome (A1C ≥6% and/or type 2 diabetes) showed trends for all prenatal exposures except parity (not shown). Findings were similar for A1C measured continuously, with the exception of increasing parity where a significantly higher mean A1C was observed; for preeclampsia and gestational age, trends in A1C were not statistically significant.

Of the potential mediators to be investigated, there was an inverse association between increasing tertiles of BGA and A1C ≥6% and/or type 2 diabetes (odds ratio [OR] 0.79 [95% CI 0.68–0.94]), while the risk of A1C ≥6% and/or type 2 diabetes increased by 19% (1.17–1.22) for each kg/m^2 increase in BMI at 45 years of age. Similarly, continuous A1C decreased by 0.03% units (−0.04 to −0.01) with each increasing tertile of BGA and increased by 0.03% (0.026–0.034) per kg/m^2 BMI.

Table 2 presents results from logistic regression analyses (n = 7,518). Moderate associations were found for all prenatal factors with A1C ≥6% and/or type 2 diabetes after simultaneous adjustment for each other and confounders, although gestational age was of borderline significance (Table 2, *column 1*). Adjustments for adult adiposity (BMI and waist circumference) reduced the associations to a greater extent than adjustments for BGA. Individually, BMI and waist circumference had a similar impact on the prenatal associations (data not presented). Most notably, adiposity reduced the associations for prepregnancy BMI ≥25 kg/m^2, smoking during pregnancy, and manual SEP between 40 and 76% (Table 2, *column 3*) with some additional contribution

Table 1—*Birth weight, BMI, A1C, and prevalence (%) of A1C ≥6% and type 2 diabetes at 45 years of age by prenatal factors in the 1958 cohort*

	% (*n*)	Mean (95% CI)*			Prevalence % (*n*)†	
		Birth weight‡ (kg)	BMI at 45 years (kg/m^2)	A1C (%)§	A1C ≥6%¶	Type 2 diabetes
Overall	100 (7,518)	3.37 (3.35–3.38)	27.30 (27.18–27.41)	5.20 (5.19–5.21)	2.61 (194)	1.32 (99)
Gestational age (weeks)						
<38	7.2 (540)	2.85 (2.80–2.89)	27.38 (26.96–27.80)	5.23 (5.18–5.29)	4.32 (23)	1.48 (8)
38–42	79.4 (5,967)	3.41 (3.40–3.42)	27.25 (27.13–27.38)	5.19 (5.18–5.20)	2.36 (139)	1.31 (78)
>42	2.6 (194)	3.53 (3.46–3.60)	27.56 (26.83–28.29)	5.22 (5.16–5.28)	2.59 (5)	0.52 (1)
Missing	10.9 (817)	3.33 (3.29–3.37)	27.56 (26.83–28.29)	5.23 (5.19–5.26)	3.35 (27)	1.47 (12)
P		<0.001	0.988	0.296	0.023	0.407
Parity						
None	36.5 (2,743)	3.28 (3.26–3.30)	27.42 (27.24–27.61)	5.20 (5.18–5.21)	2.92 (79)	1.20 (33)
1	31.2 (2,349)	3.40 (3.38–3.43)	27.07 (26.87–27.26)	5.19 (5.17–5.21)	1.98 (46)	1.32 (31)
2–3	23.4 (1,762)	3.43 (3.41–3.46)	27.25 (27.31–27.47)	5.21 (5.18–5.23)	2.48 (43)	1.53 (27)
≥4	7.4 (558)	3.41 (3.36–3.46)	27.97 (27.53–28.40)	5.26 (5.22–5.31)	3.82 (21)	1.43 (8)
Missing	1.4 (106)	3.20‡	26.35 (25.41–27.30)	5.17 (5.08–5.25)	4.72 (5)	0 (0)
P		<0.001	0.392	0.023	0.830	0.385
Preeclampsia						
No	86.9 (6,530)	3.38 (3.37–3.39)	27.26 (27.14–27.37)	5.20 (5.18–5.21)	2.42 (156)	1.27 (83)
Yes	4.4 (331)	3.19 (3.12–3.26)	28.04 (27.47–28.62)	5.24 (5.18–5.30)	5.52 (18)	1.51 (5)
Missing	8.7 (657)	3.33 (3.29–3.38)	27.31 (26.94–27.69)	5.22 (5.18–5.25)	3.10 (20)	1.67 (11)
P		<0.001	0.005	0.141	0.001	0.706
Prepregnancy BMI (kg/m^2)						
<18.5	4.1 (306)	3.18 (3.12–3.24)	26.21 (25.64–26.78)	5.22 (5.16–5.28)	2.65 (8)	1.31 (4)
18.5–24.99	67.4 (5,069)	3.35 (3.33–3.36)	26.81 (26.68–26.93)	5.18 (5.17–5.19)	2.03 (102)	1.03 (52)
25.0–29.99	17.8 (1,342)	3.46 (3.43–3.49)	28.59 (28.31–28.88)	5.26 (5.22–5.29)	4.33 (57)	2.01 (27)
≥30.0	3.8 (288)	3.53 (3.46–3.59)	30.31 (29.67–30.95)	5.27 (5.21–5.33)	3.19 (9)	2.08 (6)
Missing	6.8 (513)	3.31 (3.25–3.37)	27.67 (27.21–28.13)	5.22 (5.17–5.26)	3.58 (18)	1.95 (10)
P		<0.001	<0.001	<0.001	0.001	0.009
Smoking during pregnancy (cigarettes/day)						
Nonsmoker	58.8 (4,423)	3.42 (3.40–3.43)	27.03 (26.89–27.17)	5.19 (5.18–5.20)	2.51 (110)	1.06 (47)
Ex-smoker	7.0 (525)	3.44 (3.40–3.48)	27.17 (26.76–27.59)	5.17 (5.14–5.21)	0.97 (5)	1.71 (9)
Light (1–9)	14.5 (1,093)	3.28 (3.25–3.31)	27.57 (27.26–27.87)	5.21 (5.17–5.24)	2.89 (31)	1.83 (20)
Medium (10–19)	9.5 (718)	3.24 (3.20–3.27)	28.14 (27.75–28.52)	5.21 (5.17–5.25)	3.24 (23)	1.25 (9)
Heavy (≥20)	1.6 (124)	3.15 (3.07–3.23)	28.20 (27.33–29.07)	5.20 (5.09–5.33)	3.28 (4)	1.61 (2)
Variable	5.8 (436)	3.30 (3.26–3.35)	27.82 (27.34–28.29)	5.28 (5.22–5.33)	3.26 (14)	1.61 (7)
Missing	2.6 (199)	3.22 (3.12–3.32)	27.26 (26.52–28.01)	5.23 (5.16–5.32)	3.61 (7)	2.51 (5)
P#		<0.001	<0.001	0.02	0.07	0.10
Socioeconomic position at birth						
I and II	18.8 (1,417)	3.43 (3.40–3.46)	26.22 (25.99–26.44)	5.16 (5.14–5.18)	1.63 (23)	0.71 (10)
III nonmanual	9.8 (740)	3.40 (3.36–3.44)	26.65 (26.33–26.97)	5.16 (5.13–5.18)	1.09 (8)	0.95 (7)
III manual	48.6 (3,657)	3.35 (3.33–3.37)	27.53 (27.37–27.69)	5.20 (5.18–5.22)	2.88 (104)	1.37 (50)
IV and V	22.0 (1,654)	3.34 (3.31–3.36)	27.97 (27.72–28.23)	5.25 (5.22–5.28)	3.57 (58)	1.87 (31)
Missing	0.7 (50)	3.13 (2.85–3.41)	27.69 (26.30–29.08)	5.28 (5.14–5.42)	2.04 (1)	2.00 (1)
P		<0.001	<0.001	<0.001	<0.001	0.003

*P for linear trend (excluding missing category). †P for χ^2 trend (excluding missing category). ‡n = 7,180 with birth weight data (for those missing parity, only one had birth weight data). §Geometric mean; ¶n = 7,419 (excludes 99 subjects with type 2 diabetes). #P is for smokers versus nonsmokers.

by BGA for smoking and SEP but not prepregnancy BMI. The association for smoking was attenuated to the null. Adjustment for mediating factors did less to explain the association for preeclampsia, although there was a reduction in the association by 24% with loss of statistical significance after full adjustment. Adjustment for BGA did not reduce but strengthened the association for gestational age.

CONCLUSIONS — This study demonstrates relationships between prenatal environment and glucose homeostasis in mid-adulthood. Associations for prepregnancy BMI, smoking during pregnancy, and manual SEP were to a large extent mediated through adult size but not through birth weight, even though decreased birth weight is associated with

Table 2—*Effect of prenatal factors on A1C ≥6% (including type 2 diabetes) in midlife with adjustments for confounders* and mediators†*

	Basic model*#	Basic model + BGA†		Basic model + adult adiposity‡		Basic model + BGA and adult adiposity§	
	95% CI	95% CI	%¶	95% CI	%¶	95% CI	%¶
Prenatal factors							
Gestational age <38 vs. ≥38 weeks	1.42 (0.97–2.09)	1.42 (0.96–2.09)	0	1.52 (1.00–2.31)	23.8	1.51 (1.00–2.30)	21.4
Preeclampsia vs. no preeclampsia	1.78 (1.14–2.80)	1.71 (1.09–2.70)	−9.0	1.65 (1.02–2.69)	−16.7	1.59 (0.97–2.59)	−24.4
Prepregnancy BMI ≥25 vs. BMI <25 kg/m^2	1.90 (1.45–2.47)	1.96 (1.50–2.57)	6.7	1.25 (0.94–1.67)	−72.2	1.33 (1.00–1.77)	−63.3
Smoking vs. no smoking during pregnancy	1.33 (1.04–1.71)	1.28 (1.00–1.65)	−15.1	1.08 (0.83–1.40)	−75.8	1.01 (0.78–1.32)	−97.0
Manual vs. non-manual socioeconomic position at birth	1.87 (1.36–2.58)	1.83 (1.33–2.52)	−4.6	1.52 (1.09–2.11)	−40.2	1.46 (1.04–2.03)	−47.1
Mediators							
BGA (per tertile)	—	0.81 (0.69–0.96)	—	—	—	0.73 (0.62–0.87)	—
BMI at 45 years of age (per kg/m^2)	—	—	—	1.04 (1.00–1.09)	—	1.04 (0.99–1.08)	—
Waist circumference at 45 years of age (per cm)	—	—	—	1.07 (1.05–1.09)	—	1.07 (1.05–1.09)	—

*Mutually adjusted prenatal associations (i.e., simultaneous adjustment for gestational age, preeclampsia, maternal prepregnancy BMI, smoking during pregnancy, SEP at birth) also controlling for family history of diabetes and sex. †Adjusted for factors in basic model plus BGA. ‡Adjusted for factors in basic model plus BMI and waist circumference at 45 years of age. §Adjusted for factors in basic model plus BGA, BMI, and waist circumference at 45 years of age. ¶Data are OR (odds ratio) 95% CI and percent change from basic model OR [(OR adjusted model − OR basic model/OR basic model − 1) × 100]. #Models based on complete-case analysis had higher ORs in the basic model, and some effects decreased by different amounts after adjustment for mediators. Preeclampsia remained statistically significant: 1.90 (1.09–3.32) from 2.04 (9% reduction), SEP lost statistical significance: 1.32 (0.90–1.96) from 1.81 (60% reduction).

poor glucose control as shown elsewhere (1). Relationships with glucose metabolism in adulthood for preeclampsia and particularly preterm birth did not appear to be greatly affected by their association with either birth weight or adiposity. Thus, the results suggest that prenatal exposures are likely to have the strongest effects on glucose metabolism indirectly through their influence on adiposity over the life course (Fig. 1*B* and *G*).

Methodological considerations

The major strength of this study is the prospective follow-up over 45 years of life. The 1958 British Cohort Study collected maternal and obstetric data, mostly obtained at the time of delivery and therefore not subject to recall bias (with the exception of prepregnancy weight, which was self-reported by mothers at delivery), and measured information on important mediating factors.

A limitation is that, at 45 years of age, the cohort is too young for sufficient numbers to have been diagnosed with type 2 diabetes to facilitate an analysis with adequate statistical power. A1C is typically used to monitor long-term glucose control in individuals with diabetes but is also a useful measure in people without diabetes, as suggested by the association between A1C ≥5.5% and increased risk of cardiovascular mortality (25). Our main outcome included A1C ≥6%, which has been previously shown to be associated with increased risk of microvascular complications (17). It could be argued that the mediating effects of adiposity are due to the inclusion of type 2 diabetes and that the lack of mediating effect for BGA may be due to the inclusion of lower values of A1C in the outcome. To assess the validity of these arguments, we examined relationships between mediators (BGA, BMI, and waist circumference) and alternative outcomes for glucose metabolism and found that associations were similar for all outcomes considered (namely, A1C ≥6% including and excluding type 2 diabetes, type 2 diabetes, and continuous A1C). Moreover, the general pattern of findings for prenatal factors was confirmed in supplementary analysis of alternative outcomes. A second limitation is the reduced sample with complete data for longitudinal analysis because of sample attrition and missing data on covariates. Although sample attrition has occurred, participation at 45 years of age showed only small biases by social class at birth and adult BMI. We found that individuals with A1C ≥6% were less likely to have complete information on prenatal factors than those with A1C <6%; therefore, we used multiple imputation.

Type 2 diabetes was reported at 42 years of age as a doctor's diagnosis of type 2 diabetes, which is known to correlate well with other sources (26), or information on prescribed diabetes medication observed during the interview at 45 years of age, which as a second source of information strengthens the validity of the reported data. We had only limited information on maternal diabetes, and numbers were insufficient to assess effects of intrauterine exposure to diabetes. Using information on family history of diabetes we were able, to some extent, to control for confounding by maternal diabetes on other prenatal exposures.

Comparisons with other studies

Influences on the intrauterine environment such as maternal smoking, low prepregnancy weight, and preeclampsia have a deleterious affect on birth weight (27); however, an increasing trend toward maternal obesity and higher birth weights has been reported (28,29). The effects of prenatal exposures reach into childhood and adulthood; for example, maternal obesity (30,31), maternal smoking (4,10), and diabetes during pregnancy are associated with offspring obesity (32–34). Few studies have examined early life environment and glucose metabolism in adulthood or specifically investigated the mediating effects of adiposity, the main risk factor for type 2 diabetes.

We found a moderate association for preterm birth that was not explained by birth weight, thus supporting results from

two recent studies (11,12). We also found that the association was not mediated by later adiposity, consistent with findings from the Aberdeen Children of the 1950s cohort (12). For smoking during pregnancy, an association with glucose metabolism was observed and found to be mediated primarily through adult adiposity. Thus, we do not confirm an earlier report based on the same cohort suggesting an association for heavy smoking during pregnancy and type 2 diabetes after allowing for birth weight and adult BMI (10). However, we do show an association between maternal smoking and adult adiposity as demonstrated previously (4,10).

An association was found for preeclampsia and altered glucose metabolism in offspring during adulthood. Adjustment for birth weight and adiposity reduced the association by a small amount, and a moderate effect persisted, although statistical significance was lost. Thus, possible alternative explanations include metabolic changes in the fetus due to the preeclamptic intrauterine environment leading to an increased risk for type 2 diabetes or genetic susceptibility for preeclampsia predisposing offspring of preeclamptic mothers to hypertension, insulin resistance, and glucose intolerance (35).

Little has been reported to date regarding prepregnancy obesity and risk of diabetes in offspring, despite numerous studies reporting a link with increased birth weight and obesity in both childhood and later life (30,31). The relationship between parental obesity and childhood obesity is well known, and genes that increase the susceptibility for weight gain have been identified, suggesting that both genetic and environmental factors are important for obesity in later life (36).

In conclusion, early life exposures during the prenatal period are associated with disturbances in glucose metabolism in midlife largely because they are associated with adiposity, which in turn influences risk of disturbances in glucose metabolism.

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