PRENATAL EXPOSURES AND GLUCOSE METABOLISM IN ADULTHOOD: ARE EFFECTS MEDIATED THROUGH BIRTH WEIGHT AND ADIPOSITY?

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Running title: Mediation of prenatal effects on glucose metabolism through adiposity

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ABSTRACT

Objective: Birthweight has been associated with the risk of type 2 diabetes in several studies. We investigated whether prenatal influences on birthweight (gestational age, parity, pre-eclampsia, pre-pregnancy BMI, smoking during pregnancy and socio-economic position) were associated with glucose metabolism in midlife, and the role of birthweight-for-gestational age (BGA) and adult adiposity in mediating these associations.

Research design and methods: Data from 7518 participants of the 1958 British birth cohort with information on HbA1c at age 45y were analysed. Associations between prenatal exposures and HbA1c ≥ 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 (i) BGA only (ii) concurrent adiposity only (BMI and waist circumference) (iii) BGA plus adiposity.

Results: In the basic model, pre-eclampsia (OR=1.78, 95%CI=1.14-2.80), pre-pregnancy BMI ≥ 25kg/m² (1.90, 1.45-2.47), maternal smoking (1.33, 1.04-1.71) and manual socio-economic position (1.87, 1.36-2.58) were independently associated with HbA1c at 45y. Adjustment for BGA had little impact on the prenatal factors/HbA1c associations, whereas adjustment for adult adiposity at 45y substantially reduced associations for pre-pregnancy BMI, smoking during pregnancy and socio-economic position.

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 birthweight. Prenatal exposures are likely to have the strongest effects on glucose metabolism indirectly, through their influence on adiposity.
An inverse relationship between birthweight (as a proxy for reduced foetal growth) and measures of glucose metabolism in adulthood, including the prevalence of type 2 diabetes, has been reported from several studies. According to the thrifty phenotype hypothesis, the association between reduced foetal growth and glucose metabolism in adulthood is related to poor foetal nutrition resulting from an adverse intrauterine environment. 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. Furthermore, there may be a direct effect of smoking on obesity rather than operating indirectly through socioeconomic and lifestyle pathways in childhood.

Given the influence of prenatal exposures on established risk factors for glucose metabolism, that is birthweight 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 Figure 1. Birthweight (A) and adiposity (B) are associated with impaired glucose metabolism. In particular, those born small-for-gestational-age who becomes obese as adults are at high risk of type 2 diabetes; however, increased birthweight is associated with increased adiposity and hence poor glucose control (C). Prenatal factors may directly affect glucose control (D) or be mediated through their effects on birthweight (E+A), adiposity (G+B) or both (E+F). Socioeconomic position before and during pregnancy may be associated with glucose metabolism in adulthood through its effects on prenatal factors in addition to birthweight 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. A handful of studies have reported that maternal obesity, gestational diabetes and smoking during pregnancy 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 birthweight. However, evidence is scarce supporting independent effects for prenatal exposures and glucose metabolism in adulthood. We hypothesise that, as illustrated in Figure 1, prenatal exposures will influence glucose metabolism and that their effects will be mediated through birthweight and/or adiposity during the life course. We investigate this hypothesis using data on key prenatal influences, birthweight, adult adiposity and glucose metabolism in the 1958 British birth cohort.

**RESEARCH DESIGN AND METHODS**

**Sample**

The 1958 cohort consists of data on 17,638 participants originally enrolled in the Perinatal Mortality Survey (PMS) all born one week in March 1958 in England, Scotland and Wales, and who have been interviewed at intervals in childhood and adulthood. A further 920 immigrants with the same birth dates were recruited to the study up to age 16y. A target sample of 12,069 cohort members were invited to participate in a biomedical survey at age 45y, 9377 responded (78%). We excluded 56 individuals with type 1 diabetes and 302 immigrants who had not been included in the PMS and therefore perinatal data were not obtained. The South East Multi-Centre Research Ethics Committee gave ethical approval for the biomedical survey.

**Measures**

**Outcome**

HbA1c at 45y was measured from non-fasting venous blood samples using ion exchange high performance liquid chromatography (Tosoh A1c2.2 Glycohemoglobin Analyser, HLC-723GHB, Tosoh Corp, Tokyo, Japan) at the Department of Clinical Biochemistry,
Newcastle-upon-Tyne Hospitals NHS Trust. Results were standardised to the HbA1c assay used in the Diabetes Control and Complications Trial.(15,16) The primary outcome used was HbA1c categorised as a binary variable using a cut-off of 6%.(17,18) Given that treatment for diabetes will lower HbA1c, those with type 2 diabetes were assumed to have HbA1c ≥6 in this study. Individuals diagnosed with type 2 diabetes were identified from information collected at 42y (participants reported whether a doctor had told them that they had “non-insulin-dependent diabetes that is controlled by diet or tablets”). At the 45-year survey the nurse collected information on currently prescribed medication (through direct observation of packaging) from which we identified oral anti-diabetic drugs.

**Early life exposures**

Several prenatal factors were identified from the literature that have been shown to be associated with either birthweight, obesity in later life, cardiovascular disease or type 2 diabetes: gestational age, parity, maternal body size, smoking during pregnancy, pre-eclampsia, gestational diabetes and socio-economic position (SEP). We modelled 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 on early life exposures during the PMS at the birth of the child. Gestational age was classified as <38 weeks, 38-42 weeks and >42 weeks. Parity was defined as previous pregnancies that had reached 28 weeks of gestation; categories were 0, 1, 2-3, ≥4 pregnancies. Mother’s measured height was converted from inches to centimetres and self-reported pre-pregnancy weight was converted from stones to kilograms. Body mass index (BMI) was calculated as weight (kg)/height (m)² and categorised as <18.5, 18.5-24.99, 25.00-29.99, ≥30. Information on maternal smoking was based on smoking after the fourth month of pregnancy because, at the time, smoking was thought to exert the greatest effect on birthweight in the later stages of pregnancy.(19) Smoking was coded as never smoked (not before or after 4th month of pregnancy), ex-smokers (smoked before but not after), light (1-9/day after 4th month), medium (10-19/day) and heavy (≥20/day). Those who changed their smoking habits were classified as “variable” smokers. Pre-eclampsia was defined as albuminuria (not attributable to urinary tract infection) and diastolic blood pressure >90mmHg.(19) Of those with data at age 45y, 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 father’s occupation at birth and grouped as I&II (professional and managerial), III non-manual (unskilled), III manual (skilled), IV&V (semi and unskilled manual). Single mother households were classified as IV&V. Where data were missing, father’s SEP when the child was 7y old.

**Potential mediating factors**

Birthweight was measured in pounds and ounces and converted into grams. For use in statistical modeling, birthweight was standardised for sex and gestational age (BGA) and expressed as z-score tertiles. A nurse using a standardised protocol and equipment (scales and stadiometer) measured height and weight of cohort members at 45y, without shoes and in light clothing. BMI was calculated as previously described. Waist circumference (cms) 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, 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 to the end of December 2003, and coded according to the International Classification of Diseases (10th revision) codes E10 to E14.(20)

**Analysis**
Analyses were conducted using STATA version 9.2. Univariate relationships between prenatal factors, birthweight, BMI and HbA1c were first explored: linear trends in the prevalence of HbA1c≥6 and type 2 diabetes across categories of prenatal exposures were assessed using chi-squared trend tests and variation in continuous measures (birthweight, BMI, HbA1c) were tested by entering each prenatal variable as a continuous variable into regression models. HbA1c was log transformed and geometric means presented; robust estimation was used in regression models of HbA1c because the homoscedasticity assumption could not be met through transformation.(21)

The role of BGA and adiposity as mediators of prenatal factor-HbA1c associations was investigated using a series of logistic regression models. First, a basic model was fitted consisting of all prenatal variables simultaneously that were significantly associated with the main outcome, HbA1c≥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 (i) BGA, (ii) adiposity at 45y (BMI, waist circumference separately and together) (iii) BGA and adiposity. Quadratic as well as linear terms for the mediators were tested because BMI and waist circumference had curvilinear associations with HbA1c, and collinearity was tested using the variance inflation factor (VIF). Prenatal exposures were modelled as dichotomous variables because the number with HbA1c≥6 and/or type 2 diabetes was small in several of the exposure categories. Gender interactions were investigated for the 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: (i) diagnosed type 2 diabetes, and (ii) HbA1c≥7 (because this is 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 (HbA1c≥6 and/or type 2 diabetes) are presented here.

Missing data

Data at 45y were available on HbA1c, BMI and waist circumference for 7518 individuals. The sample was broadly similar to the original birth population: for SEP at birth, 19.0% of the analysis sample compared to 17.2% of the original population was in classes I & II; 22.2% compared to 24.5% respectively in classes IV & V. There was also a modest under-representation at 45y of those with a higher BMI at 33y: the sample with data at 45y was 0.5kg/m² lower than those without data. 5673 of 7518 participants had complete data on prenatal factors and BGA. Those with HbA1c≥6 and/or type 2 diabetes had more missing data than those with HbA1c<6 (32% vs 24.7%, χ²=9.4, p=0.002). We therefore imputed the missing covariates using the “mice” method (multiple imputation by chained equations) described by Van Buuren.(23) As recommended, 10 copies of the original dataset imputed for missing data were created and a regression analysis that combines 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 birthweight, BMI at 45y and glucose metabolism at 45y. The geometric mean HbA1c 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 HbA1c≥6 was 2.61%; for type 2 diabetes it was 1.32%. Increasing gestational age, parity, and pre-pregnancy BMI were associated with higher birthweight, whereas, pre-eclampsia, smoking during pregnancy and lower SEP, were associated with lower
birthweight. Similar trends were seen for BGA (data not shown). All except gestational age and parity were significantly associated with increased BMI in adulthood. A trend for increasing prevalence of HbA1c≥6 (excluding type 2 diabetes) was found for lower gestational age, pre-eclampsia, higher pre-pregnancy BMI and lower SEP. Results were similar for type 2 diabetes except that trends for gestational age and pre-eclampsia were not statistically significant. An increased prevalence for either HbA1c≥6 or type 2 diabetes existed for smoking during pregnancy, but was only statistically significant for the two outcomes combined. The combined outcome (HbA1c≥6 and/or type 2 diabetes) showed trends for all prenatal exposures except parity (not shown). Findings were similar for HbA1c measured continuously, except for increasing parity where significantly higher mean HbA1c was observed; and for pre-eclampsia and gestational age trends in HbA1c were not statistically significant.

Of the potential mediators to be investigated, there was an inverse association between increasing tertiles of BGA and HbA1c≥6 and/or type 2 diabetes; (odds ratio=0.79, 0.68-0.94) while the risk of HbA1c≥6 and/or type 2 diabetes increased by 19% (1.17-1.22) for each kg/m^2 increase in BMI at 45y. Similarly, continuous HbA1c decreased by 0.03 %units (-0.04, -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=7518). Moderate associations were found for all prenatal factors with HbA1c≥6 and/or type 2 diabetes after simultaneous adjustment for each other and confounders, although gestational age was of borderline significance (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 pre-pregnancy BMI≥25, smoking during pregnancy and manual SEP between 40 and 76% (column 3) with some additional contribution by BGA for smoking and SEP but not pre-pregnancy BMI. The association for smoking was attenuated to the null. Adjustment for mediating factors did less to explain the association for pre-eclampsia, 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**

**Summary of results**

This study demonstrates relationships between prenatal environment and glucose homeostasis in mid-adulthood. Associations for pre-pregnancy BMI, smoking during pregnancy and manual SEP were to a large extent mediated through adult size but not through birthweight, even though decreased birthweight is associated with poor glucose control as shown elsewhere.(1) Relationships with glucose metabolism in adulthood for pre-eclampsia and particularly pre-term birth did not appear to be greatly affected by their association with either birthweight 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 (Figure 1, pathway G+B).

**Methodological considerations**

The major strength of this study is the prospective follow-up over 45 years of life. The 1958 cohort study has detailed maternal and obstetric data, mostly collected at the time of delivery and therefore not subject to recall bias, (an exception is pre-pregnancy weight that was self-reported by mothers at the time of delivery) and measured information on important mediating factors.

A limitation is that, at 45y 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. HbA1c is typically used to monitor long-term glucose control.
In the context of glucose control in people with diabetes, but is also a useful measure in people without diabetes as suggested by the association between HbA1c ≥ 5.5 and increased risk of cardiovascular mortality. Our main outcome included HbA1c ≥ 6%, previously shown to be associated with increased risk of microvascular complications. It could be argued, that the mediating effects of adiposity are due to the inclusion of type 2 diabetes, in the outcome, and the lack of mediating effect for BGA may be due to the inclusion of lower values of HbA1c 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, HbA1c ≥ 6 including and excluding type 2 diabetes, type 2 diabetes, continuous HbA1c). Moreover, the general pattern of findings for prenatal factors was confirmed in supplementary analyses 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 45y showed only small biases by social class at birth and adult BMI. We found individuals with HbA1c ≥ 6 were less likely to have complete information on prenatal factors than those with HbA1c < 6, therefore we used multiple imputation.

Type 2 diabetes was reported at 42y as a doctor’s diagnosis of type 2 diabetes, which is known to correlate well with other sources, or information on prescribed diabetes medication observed during the 45y interview, 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, but 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 pre-pregnancy weight and pre-eclampsia have a deleterious affect on birthweight, however, an increasing trend towards maternal obesity and higher birthweights has been reported. The effects of prenatal exposures reach into childhood and adulthood; for example, maternal obesity, maternal smoking, and diabetes during pregnancy are associated with offspring obesity. 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 birthweight, thus supporting results from two recent studies. We also found that the association was not mediated by later adiposity, consistent with findings from the Aberdeen Children of the 1950s cohort. For smoking during pregnancy, an association with glucose metabolism was observed that was 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 birthweight and adult BMI. However, we do show an association between maternal smoking and adult adiposity as demonstrated previously.

An association was found for pre-eclampsia and altered glucose metabolism in offspring during adulthood. Adjustment for birthweight 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 foetus due to the pre-eclamptic intrauterine environment leading to an increased risk for type 2 diabetes, or genetic susceptibility for pre-eclampsia predisposes offspring of pre-eclamptic mothers to hypertension, insulin resistance and glucose intolerance.

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

**Conclusions**

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.

**ACKNOWLEDGEMENTS**

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Reference List


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<td>27.69 (26.30-29.08)</td>
<td>5.28 (5.14-5.42)</td>
<td>2.04 (1) (2.00 (1))</td>
</tr>
</tbody>
</table>

*P-value for linear trend (excluding missing category)

†P-value for chi-squared trend (excluding missing category)

‡N=7180 with birthweight data. Note for those missing parity, only 1 had birthweight.

§geometric mean

ⁿ=7419 (excludes 99 with T2DM)

□p-value is for smokers versus non-smokers

* Socio-economic position
Table 2: Effect of prenatal factors on HbA1c ≥ 6 (including type 2 diabetes) in midlife with adjustments for confounders* and mediators§: odds ratios (OR) and 95% confidence intervals (N=7518)

<table>
<thead>
<tr>
<th>Prenatal factors</th>
<th>Basic model *#</th>
<th>Basic model plus birthweight-for-gestational age †</th>
<th>Basic model plus adult adiposity ‡</th>
<th>Basic model plus birthweight-for-gestational age &amp; adult adiposity §</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>%¶ OR (95% CI)</td>
<td>%¶ OR (95% CI)</td>
</tr>
<tr>
<td>Gestational age &lt;38 weeks vs ≥ 38 weeks</td>
<td>1.42 (0.97-2.09)</td>
<td>1.42 (0.96-2.09)</td>
<td>0</td>
<td>1.52 (1.00-2.31)</td>
</tr>
<tr>
<td>Pre-eclampsia vs no pre-eclampsia</td>
<td>1.78 (1.14-2.80)</td>
<td>1.71 (1.09-2.70)</td>
<td>-9.0</td>
<td>1.65 (1.02-2.69)</td>
</tr>
<tr>
<td>Pre-pregnancy BMI ≥ 25 vs BMI &lt; 25</td>
<td>1.90 (1.45-2.47)</td>
<td>1.96 (1.50-2.57)</td>
<td>6.7</td>
<td>1.25 (0.94-1.67)</td>
</tr>
<tr>
<td>Smoking vs no smoking during pregnancy</td>
<td>1.33 (1.04-1.71)</td>
<td>1.28 (1.00-1.65)</td>
<td>-15.1</td>
<td>1.08 (0.83-1.40)</td>
</tr>
<tr>
<td>Manual vs non-manual SEP at birth</td>
<td>1.87 (1.36-2.58)</td>
<td>1.83 (1.33-2.52)</td>
<td>-4.6</td>
<td>1.52 (1.09-2.11)</td>
</tr>
<tr>
<td>Mediators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight-for-gestational age (per tertile)</td>
<td>-</td>
<td>0.81 (0.69-0.96)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMI 45y (per kg/m²)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Waist circumference 45y (per cm)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.07 (1.05-1.09)</td>
</tr>
</tbody>
</table>

*Mutually adjusted prenatal associations (i.e. simultaneous adjustment for gestational age, pre-eclampsia, maternal pre-pregnancy BMI, smoking during pregnancy, SEP at birth), controlling also 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.
§Adjusted for factors in basic model plus BGA, BMI and waist circumference at 45 years.
¶percentage 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. Pre-eclampsia 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).
Figure 1 – legend

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.
E. (+A) Effect of prenatal factors on glucose control, mediated through birthweight.
G. (+B) Effect of prenatal factors on glucose control, mediated through adiposity.
E. (+F) Effect of prenatal factors on glucose control, mediated through both birthweight and adiposity.

Socioeconomic position before and during pregnancy may influence glucose metabolism through its effects on prenatal factors and/or through effects on birthweight and adiposity.

Figure 1: Hypothesised relationships between early life environment, birth weight, adiposity and glucose metabolism in adulthood