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Original Article: Metabolism

Offspring birth weight, gestational age and maternal characteristics in relation to glucose status at age 53 years: evidence from a national birth cohort


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Abstract

Aims We investigated pathways linking offspring birth weight to maternal diabetes risk in later life by taking into account a range of prospective early-life and adult maternal factors.

Methods In a national birth cohort study, we examined the relationship between offspring birth weight and maternal glycated haemoglobin (HbA\textsubscript{1c}) at age 53 years in 581 mothers who had a first birth between age 19 and 25 years, and had data on potential confounders or mediators.

Results Mean age at first birth was 21.5 years. After adjustment for maternal body mass index (BMI), mean percentage change in maternal HbA\textsubscript{1c} per kilogram increase in offspring birth weight was \(-1.8\%\) [95% confidence interval (CI) \(-3.5, -0.1\); \(P = 0.03\)]. This relationship was mostly accounted for by gestational age that was inversely related to maternal HbA\textsubscript{1c} (\(-0.9\%\); 95% CI \(-1.5, -0.4\); \(P = 0.001\)). Other risk factors for high HbA\textsubscript{1c} were smoking and high BMI at 53 years. There was a significant interaction between offspring birth weight and maternal childhood social class (\(P = 0.01\)). Mothers from a manual background with higher birth weight offspring had lower HbA\textsubscript{1c} (BMI adjusted: \(-3.1\%\); 95% CI \(-5.0, -1.1\)); this was not observed for mothers from a non-manual background (BMI adjusted: 1.9%; 95% CI \(-1.3, -5.0\)).

Conclusions Short gestational age and low offspring birth weight may be part of a pathway linking impaired early maternal growth to diabetes risk in later life. A second possible pathway linking higher offspring birth weight to later maternal glucose status was also identified. These potential pathways require further investigation in cohorts with a wider maternal age range so that the early targeting of public health initiatives can be assessed.


Keywords gestational age, glucose intolerance, HbA\textsubscript{1c}, maternal birth weight, offspring birth weight

Abbreviations BMI, body mass index; HbA\textsubscript{1c}, glycated haemoglobin; MRC, Medical Research Council

Introduction

Reproductive function, in terms of menstrual patterns, age at first pregnancy, parity and pregnancy outcome, is not only integral to women’s overall health and wellbeing from menarche to menopause, but is increasingly recognized as a sentinel of chronic disease in later life [1].

With regard to pregnancy outcomes, a series of studies has shown that mothers of smaller babies tend to live shorter lives, and are more likely to die from cardiovascular disease [2,3]. They are also more likely to have diabetes and/or insulin resistance in later life [4–6]; these are important risk factors for cardiovascular disease. Some studies show a "U"-shaped association between offspring birth weight and subsequent diabetes risk.

The associations between lower offspring birth weight and increased risk of maternal diabetes and cardiovascular disease do not appear to be explained by adult maternal characteristics, such as smoking or socioeconomic disadvantage, which could...
both lower the birth weight of offspring and increase chronic disease risk. Nor do these associations appear to be due to shorter gestational age or other pregnancy complications that may result in a baby of lower birth weight, although in one study offspring gestational age accounted for some of the inverse relationship between offspring birth weight and maternal diabetes mortality [6]. The inverse association between offspring birth weight and maternal diabetes and cardiovascular risk could also reflect biological programming during the mother’s own prenatal or early postnatal growth periods that subsequently affects both her pregnancy outcome [1] and her risk of chronic disease [7]. The upturn in risk for mothers of the heaviest babies in studies that show a U-shaped relationship between offspring birth weight and maternal diabetes [4,6] probably reflects a group of women with gestational diabetes having heavier babies and being at greater risk of diabetes later in life [8].

We examined the relationship between glycated haemoglobin (HbA1c) at age 53 years and the birth weight of first-born offspring in mothers participating in the Medical Research Council (MRC) National Survey of Health and Development, a prospective UK birth cohort study. HbA1c corresponds to mean plasma glucose concentrations and high HbA1c affects diabetes risk in people without diabetes [9]. The benefits of this study are the prospective data on offspring gestational age, the mother’s own birth weight, lifetime socioeconomic position, adult smoking habits, height, weight, and weight change since early adult life; they allow us to test possible explanations for any observed association between offspring birth weight and maternal HbA1c.

Material and methods

The MRC National Survey of Health and Development is a cohort of 2547 women and 2815 men followed since their birth in March 1946, so far until age 53 years [10,11]. The sample remains generally representative of the British population born at the same time [11]. When cohort members were aged between 19 and 25 years, a study of first-born offspring to women only was undertaken [12]. By 25 years of age, 1260 women had become mothers, of whom 1004 participated in the second-generation study. Data on birth weight recorded to the nearest quarter pound, gestational age were extracted from the confinement records of these women. There were 996 mothers whose first pregnancy resulted in a singleton birth for whom birth weight was known. The mean birth weight for singletons was 3.32 kg for male offspring and 3.20 kg for female offspring. This weight was known. The mean birth weight for singletons was 3.32 kg for male offspring and 3.20 kg for female offspring. This model was used to adjust the relationship between offspring birth weight and maternal HbA1c. In this way the observed values of the diabetic women were censored, so that the actual unobserved values were assumed to be at least that value or higher. The natural logarithm of HbA1c (>100) was used to reduce the right skewness of the distribution. Therefore the regression coefficients in these models can be interpreted as symmetric percentage change in HbA1c [13].

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This model was used to adjust the relationship between offspring birth weight and maternal HbA1c for maternal BMI at 53 years. Possible confounding or mediating factors, namely offspring gestational age, maternal birth weight, height, smoking, parity, and child and adult social class were then added in turn.
HbA in models with birth weight and childhood or adult social class adjusting for gestational age (Table 2). There was no evidence that there was a stronger effect of offspring birth weight on maternal Hba1c for women with shorter pregnancies (P-value for the interaction term = 0.5).

Maternal birth weight and maternal height increased steadily across the offspring birth weight groups (Table 1). Adjusting for these factors only slightly reduced the effect of offspring birth weight on maternal Hba1c (Table 2). Women who had lighter babies were also more likely to smoke and to come from the manual classes in childhood and adult life (Table 1). Adjusting for maternal smoking or adult social class reduced the effect of offspring birth weight on maternal Hba1c (Table 2). There was evidence of an interaction between childhood social class and offspring birth height (Table 3) such that the relationship between offspring birth weight and maternal Hba1c was negative for those from a manual social class but positive for those from a non-manual social class: percent change in Hba1c per kg increase in offspring birth weight for those from a manual background was −3.06% (−5.03, −1.08) and percent change for those from a non-manual background was 1.87% (−1.29, 5.04). There was no evidence of an interaction between offspring birth weight and adult social class (P-value for interaction = 0.3). Maternal parity was not associated with the birth weight of first-born offspring (Table 1), and adjusting for parity slightly reduced the association between offspring birth weight and maternal Hba1c (Table 2).

The final model showed no effect of offspring birth weight on maternal Hba1c after adjusting for all other factors (Table 4). The most important factors associated with a higher maternal Hba1c were a higher maternal BMI (P < 0.001), smoking (P = 0.002) and shorter gestational age in first-born offspring (P = 0.01). The P-value for the interaction term between childhood social class and offspring birth weight remained significant (P = 0.02) when added to the final model.

### Table 1 Characteristics (means and percentages) of women by offspring birth weight (N = 581)

<table>
<thead>
<tr>
<th>Offspring birth weight</th>
<th>Hba1c (%) (geometric mean)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.92 kg (n = 136)</td>
<td>5.69</td>
<td>0.08</td>
</tr>
<tr>
<td>2.92–3.23 kg (n = 123)</td>
<td>5.69</td>
<td></td>
</tr>
<tr>
<td>3.23–3.54 kg (n = 170)</td>
<td>5.63</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.54 kg (n = 150)</td>
<td>5.59</td>
<td></td>
</tr>
</tbody>
</table>

The geometric mean for Hba1c was 5.64%.

*On diabetic medication, doctor diagnosed diabetes.
†Odds ratios from logistic regression.

To test whether change in BMI between 20 and 53 years of age affected the relationship between offspring birth weight and maternal Hba1c, we substituted BMI at age 53 with BMI at age 20 and 53 years of age. To test whether an effect of offspring birth weight on maternal Hba1c was modified by social circumstances in childhood or adult circumstances, we included an interaction term (gestational age × offspring birth weight) in a model with the two main effects and maternal Hba1c affected the relationship between offspring birth weight and maternal Hba1c was modified by social circumstances in childhood or adult circumstances. All potential confounders or mediators were then entered or adult circumstances than for those in better circumstances (Table 2). There was no evidence of an interaction between childhood social class and offspring birth weight (Table 2). There was no evidence of an interaction between offspring birth weight and maternal Hba1c for women with shorter pregnancies (P-value for the interaction term = 0.5).

### Results

Maternal Hba1c at age 53 years decreased by −1.52% (95% confidence interval −3.23, 0.19; P = 0.08) per kg change in birth weight (Table 1). After adjusting for maternal BMI at age 53 years, this relationship became stronger, with maternal Hba1c decreasing by −1.80% (−3.46, −0.14) per kg change in birth weight (P = 0.03) (Table 2). The effect of change in BMI between 20 and 53 years of age on the relationship between offspring birth weight and maternal Hba1c was similar (not shown). Gestational age was strongly associated with birth weight (Table 1) and inversely associated with maternal Hba1c (−0.90%; −1.45, −0.35; P = 0.001) for each additional week of gestation. The percentage difference in maternal Hba1c for a kg change in birth weight was considerably reduced after adjusting for gestational age (Table 2). There was no evidence

In this cohort of mothers who had a first birth between 19 and 25 years of age, gestational age rather than low birth weight was associated with higher maternal HbA1c in late middle age. Compared with previous studies that have found an inverse relationship between offspring birth weight and diabetes risk [4–6,18], our unadjusted findings are consistent, albeit
This study had the advantage of including a range of prospectively collected life course factors not always available in previous cross-sectional studies [4,6,18]. The most important was gestational age, which strongly reduced the association between offspring birth weight and maternal HbA\textsubscript{1c}. A recent Swedish record linkage study also found an inverse association between gestational age and maternal diabetes mortality and that the effect of gestational age reduced the association between offspring birth weight and maternal diabetes mortality [6]. Another study [5] has reported associations between offspring birth weight and maternal diabetes mortality. Another limitation [6] of this study is the lack of data on father’s offspring, which would have provided an opportunity to unravel differences between the paternal and maternal influences on offspring birth weight and diabetes risk.

In conclusion, this study has used prospective data to investigate the link between offspring birth weight and maternal HbA\textsubscript{1c} in late middle age, taking into account a broad range of maternal factors across the life course. The results show that gestational age rather than low birth weight was associated with higher maternal HbA\textsubscript{1c} and this may be part of a pathway linking impaired early maternal growth to diabetes risk in later life. A second possible pathway linking higher offspring birth weight to later diabetes risk in women from a non-manual social class was also identified. The relative importance of these two pathways needs to be investigated in older and younger birth cohorts and in samples with a wider maternal age range. Research should also focus on the underlying genetic and environmental mechanisms that determine the pathways and assess the potential role for early targeting of public health initiatives.

Contributors
D.K. conceptualised the paper, drafted and edited the manuscript. G.D.M. reviewed the literature and assisted with drafting and editing of the manuscript. L.O. conducted some of the statistical analysis. S.B. and R.H. provided advice regarding the statistical methods and interpretation of the results. D.A.L. and G.D.S. contributed to the development of the study hypothesis and provided advice regarding interpretation of the results and assisted with editing of the manuscript. M.E.J.W. was responsible for data collection and edited the manuscript.

Competing interests
None to declare.

References


