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DOI: 10.1136/bmj.325.7360.359

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Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey
Debbie A Lawlor, George Davey Smith, Shah Ebrahim

Abstract
Objective To investigate the association between birth weight of offspring and mothers' insulin resistance in late adulthood.
Design Cross sectional survey.
Setting General practitioner's surgeries in 23 towns in Great Britain.
Participants 4286 women aged 60-79 years.
Main outcome measures Maternal insulin resistance.
Results Birth weight of offspring was inversely related to maternal insulin resistance in late adulthood. For each 1 kg higher birth weight of offspring, women had a 15% reduction in the odds of being in the fourth with highest insulin resistance, compared to other fourths (odds ratio 0.85; 95% confidence interval 0.71 to 1.00). This increased to 27% (0.73; 0.60 to 0.90) after adjusting data for potential confounders. A U shaped relation between birth weight of offspring and diabetes in older age was found; women with the lightest and heaviest offspring had the highest prevalence of diabetes.
Conclusions Birth weight of offspring is inversely related to the mother's insulin resistance in late adulthood, despite the association of glucose intolerance during pregnancy with heavier offspring at birth. Common genetic factors contribute to the relation between birth weight and risk of cardiovascular disease and diabetes in adults.

Introduction
Low birth weight is associated with cardiovascular disease and type 2 diabetes in adulthood, but the mechanisms underlying these associations are unclear. Poor intrauterine nutrition leads to babies with low birth weight and may "programme" selective changes in body composition, hormonal axes, and metabolism, leading to increased risk of cardiovascular disease in later life. Alternatively, the fetal insulin hypothesis suggests that the specific genetic polymorphisms lead to increased insulin resistance and impaired growth and that these polymorphisms underlie the association between birth weight and cardiovascular disease. Studies have shown that low birth weight of offspring is related to an increased risk of cardiovascular disease and diabetes in the parents.

The relation between low birth weight and later risk of disease in the individual may be explained by a programming effect of the intrauterine environment, but the relation between a baby's low birth weight and its parents' risk must have a different explanation: a plausible explanation for these transgenerational associations is that birth weight and cardiovascular disease are linked by a common genetic factor.

No previous study has directly assessed the fetal insulin hypothesis by looking at the association between birth weight of offspring and parental insulin resistance. Mothers with gestational glucose intolerance tend to have heavier babies, and since these mothers are more likely to be insulin resistant and to develop diabetes later in life, the expectation is of a positive correlation between birth weight of offspring and maternal insulin resistance. If an inverse association between birth weight of offspring and parental insulin resistance exists, particularly in mothers, it would support the fetal insulin hypothesis. We investigated the associations between offspring birth weight and maternal insulin resistance in late adulthood.

Participants and methods
The British women's heart and health study is a sample of 60-79 year old women, randomly selected from general practitioners' lists in 23 towns in Great Britain. We selected towns, general practitioners, and participants in the same way as for the British regional heart study of men. Of the 7143 women invited, 4286 (60%) participated. We collected baseline data (via questionnaires, interviewing by a research nurse, and examinations) between April 1999 and March 2001. Ethics committee approval was obtained for the British women's heart and health study.

Details of all measurements are published elsewhere. Participants were asked how many pregnancies and live births they had experienced. We asked women with at least one live birth to provide the sex and birth weight of their first born child. We took fasting blood samples and estimated insulin resistance with the homoeostasis model assessment (the product of fasting glucose and insulin concentrations (in mmol/l) divided by 22.5). We considered women with a clinical diagnosis of diabetes and women with a fasting glucose concentration of ≥8 mmol/l to have diabetes, for the purpose of this study. Homoeostasis model assessment scores are not valid for these women, and were not calculated.
Results

Of the 4286 women who participated, 3849 (90%) provided obstetric details. Of the 3456 (90%) women who had had at least one live birth, 3289 (94%) provided their firstborn’s birth weight. For 24 women, birth weight of offspring was less than 1.5 kg; they were excluded. Of the 3265 women with offspring birth weight included in the analysis 1635 (50.1%) of the children were male with a mean birth weight of 3.38 (SD 0.53) kg and 1630 (49.9%) were female with a mean birth weight of 3.24 (0.51) kg. A total of 169 (5.2%) women had been diagnosed with diabetes by a doctor and 41 (1.3%) had a glucose concentration after fasting of ≥8 mmol/l.

The table gives the relations between birth weight of offspring and age adjusted insulin resistance scores and other risk factors for cardiovascular disease, together with regression coefficient or odds ratios for each variable per kilogram difference in offspring birth weight. Women who had heavier babies were less resistant to insulin, had lower systolic blood pressure, had a higher body mass index, were less likely to smoke, and were more likely to belong to non-manual social classes both in childhood and adulthood.

Offspring birth weight was not linearly associated with maternal diabetes prevalence; women who had had babies with birth weights in the lowest and highest quarters were most likely to be diabetic in older age. When a quadratic term for birth weight of offspring was fitted, this model suggested a non-linear association (P=0.08). The relation between diabetes prevalence and birth weight of offspring was unaffected by control for current body mass index. The inverse relation between offspring birth weight and maternal insulin resistance contradicted the positive relation between birth weight of offspring and maternal body mass index. For each increase of 1 kg to offspring birth weight, the logarithm of the insulin resistance scores fell by 0.04, whereas body mass index (weight/(height(m))^2) increased by 0.74.

The odds of maternal insulin resistance (top quartile of birth weights compared with all other participants, adjusted by age) decreased with increasing

Relation of maternal characteristics to birth weight of offspring

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Fourth of offspring birth weight (kg)</th>
<th>Age adjusted difference per kg offspring birth weight</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.56-2.94</td>
<td>2.95-3.26</td>
<td>3.27-3.58</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.4 (68.1 to 68.8)</td>
<td>68.4 (68.1 to 68.8)</td>
<td>68.7 (68.4 to 69.2)</td>
</tr>
<tr>
<td>Insulin resistance (HOMA score)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.75 (1.67 to 1.83)</td>
<td>1.61 (1.54 to 1.69)</td>
<td>1.67 (1.59 to 1.75)</td>
</tr>
<tr>
<td>Diabetes (%)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>8.1 (6.3 to 10.3)</td>
<td>7.5 (5.7 to 9.7)</td>
<td>6.3 (4.7 to 9.7)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>149.5 (147.8 to 151.2)</td>
<td>147.3 (145.6 to 149.1)</td>
<td>145.8 (144.1 to 147.5)</td>
</tr>
<tr>
<td>HDLc (mmol/l)</td>
<td>1.64 (1.61 to 1.67)</td>
<td>1.68 (1.63 to 1.69)</td>
<td>1.68 (1.65 to 1.72)</td>
</tr>
<tr>
<td>LDLc (mmol/l)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4.17 (4.09 to 4.25)</td>
<td>4.15 (4.07 to 4.23)</td>
<td>4.17 (4.09 to 4.25)</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.70 (1.65 to 1.76)</td>
<td>1.63 (1.58 to 1.68)</td>
<td>1.65 (1.59 to 1.71)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.2 (26.9 to 27.6)</td>
<td>27.2 (26.9 to 27.6)</td>
<td>27.5 (27.3 to 28.0)</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.817 (0.813 to 0.822)</td>
<td>0.817 (0.812 to 0.821)</td>
<td>0.816 (0.811 to 0.820)</td>
</tr>
<tr>
<td>Ever smoked (%)</td>
<td>52.9 (49.5 to 56.3)</td>
<td>51.8 (48.1 to 55.0)</td>
<td>49.0 (45.6 to 52.5)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>14.31 (12.1 to 16.8)</td>
<td>10.7 (8.7 to 13.0)</td>
<td>10.5 (8.6 to 12.8)</td>
</tr>
</tbody>
</table>

HOMA=homoeostasis model assessment score. HDLc=high density lipoprotein cholesterol. LDLc=low density lipoprotein cholesterol.

† Doctor diagnosis of diabetes or fasting glucose ≥8 mmol/l.

1 Difference per kg of offspring birth weight: regression coefficients for continuous variables to odds ratios per kilogram of offspring birth weight for binary variables.

‡ Doctor diagnosis of diabetes or fasting glucose ≥8 mmol/l.

1 Geometric mean and logodds regression coefficient.
Discussion
Birth weight of offspring is inversely related to maternal insulin resistance in later life. This supports the fetal insulin hypothesis, which says that genetic factors related to both insulin resistance and birth weight explain at least part of the relation between birth weight and risk of adult cardiovascular disease and diabetes.

Although the proportion of women with gestational diabetes may be insufficient to account for a population effect on the distribution of birth weight, there is evidence that gestational glycaemia across the population distribution (rather than a simple diabetic threshold effect) is positively associated with offspring birth weight and insulin resistance and frank diabetes in the mother in later life. Although the mean cholesterol concentration, systolic blood pressure, smoking prevalence, and diabetes prevalence for women in our study are similar to those for older women in the health survey for England, the mean cholesterol concentration, systolic blood pressure, smoking prevalence, and diabetes prevalence for women in our study are similar to those for older women in the health survey for England.
practitioners and their staff who have supported data collection and the women who have participated in the study.

Contributors: All the authors developed the study aim and design. DAL undertook the initial analysis and coordinated writing of the paper. All authors contributed to the final version. DAL is guarantor.

Funding: The British women's heart and health study is funded by the Department of Health. DAL is funded by a Medical Research Council and Department of Health training fellowship. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health or MRC.

Competing interests: None declared.