Birthweight and fasting glucose and insulin levels: results from the Aboriginal Birth Cohort Study

The concerning rise in type 2 diabetes in Indigenous populations continues, with different hypotheses put forward to explain the phenomenon. International evidence links the fetal nutrition proxies of low birthweight (LBW) and fetal growth restriction (FGR) to chronic diseases in adult life. The developmental origins of health and disease (DOHaD) hypothesis states that undernutrition in utero results in permanent changes through epigenetic mechanisms that later influence disease development (http://www.mrc.soton.ac.uk/dohad). The highest risk for type 2 diabetes is reported when LBW or FGR is followed by later overweight or obesity, suggesting a mismatch between intrauterine and postnatal nutrition.

Despite recent improvements, Australian Aboriginal LBW rates remain double those of the non-Aboriginal population. National Aboriginal rates of FGR are unknown, but in a Northern Territory study, 25% of Aboriginal newborns were defined as fetal growth restriction.

Concurrently, not only are Australian Indigenous rates of overweight and obesity increasing — they currently range from 37% for ages 15–24 years to 74% for those aged over 55 years — but 10%–30% of Aboriginal people are now estimated to have type 2 diabetes.

The high-risk combination of LBW and later obesity has been shown to be the greatest risk for elevated blood pressure in a cross-sectional community study of a NT Aboriginal population. More recently, a retrospective study in one NT community linked LBW and later chronic disease in Australian Aboriginal people and suggested LBW may be a contributor to the current high rates of type 2 diabetes in the Aboriginal population.

Using data from a prospective life-course Aboriginal birth cohort study, our aim was to examine the relationships of glucose and insulin metabolism with birth and current adolescent size.

Methods
We conducted a prospective life-course study of an NT Aboriginal birth cohort.

The recruitment and follow-up of this birth cohort has been previously published. In brief, 686 Aboriginal babies out of a possible 1238 born at the Royal Darwin Hospital (1987–1990) were recruited into the study. There were no significant differences in the mean birthweight, sex ratio or birthweight frequencies between those recruited (686), those with gestational age estimation (603) and those not recruited. At follow-up (2005–2008) in over 40 NT locations, 68 participants could not be found (9.9%). Of the remainder, 27 had died, 11 refused consent, 111 were traced but were unable to be examined for logistical reasons, and 469 who had complete perinatal and adolescent data were examined.

The birth measures of weight, gestational age estimations and follow-up anthropometric measures have previously been described. Within 4 days of birth, the same neonatal paediatrician performed a gestational age assessment using the Dubowitz scoring system. LBW was defined as birthweight <2500 g, FGR as birthweight <10th percentile for gestational age, and large for gestational age as birthweight >90th percentile for gestational age, using an Australian population reference standard contemporary with cohort recruitment.

Adolescents were measured in light clothing while barefoot. Height was measured to the nearest millimetre using a portable stadiometer and weight was measured to the last complete 0.1 kg with a digital electronic scale (TBF-521, Tanita). Participants were asked to fast from midnight before the examination. Blood samples were taken at the time of examination, collected in fluoride oxalate tubes after application of anaesthetic cream to the venepuncture site, separated after collection (for a minority of samples, this was up to a maximum of 2–3 hours) and transported in cold-boxes to Darwin.

Fasting glucose levels were measured enzymatically using a modular analyser (Roche Diagnostics), fasting insulin levels were measured by

Abstract

Objective: To examine the relationships between birthweight, current size, and fasting glucose and fasting insulin levels in Aboriginal adolescents.

Design, participants and setting: Longitudinal prospective study of a Northern Territory Aboriginal birth cohort of 686 Aboriginal babies born at the Royal Darwin Hospital between January 1987 and March 1990, and followed up between December 2006 and January 2008 in over 40 NT locations.

Main outcome measures: Fasting insulin and glucose levels, adjusted for gestational age, sex and contemporary age.

Results: Among the 134 participants with complete data, those with fetal growth restriction (FGR) or low birthweight (LBW) at birth were not overweight at 18 years. In these circumstances, birthweight showed a significant positively directed association with fasting glucose levels ($P = 0.002$). Current weight showed a significant and positively directed association with both fasting insulin ($P < 0.001$) and fasting glucose levels ($P = 0.001$), and current height showed a significant and positively directed association with insulin levels ($P = 0.006$).

Conclusions: Birthweight was only positively associated with fasting glucose levels, with no association with fasting insulin levels. The high-risk combination for type 2 diabetes of LBW or FGR with later overweight or obesity was rare in this adolescent Aboriginal population.
immunoassay (AxSYM, Abbott Laboratories), and glycated haemoglobin concentrations by high-pressure liquid chromatography (PDQ, Primus Diagnostics). Insulin resistance was estimated from fasting insulin and glucose concentrations using homeostatic model assessment (HOMA-IR).\textsuperscript{13}

Cross-sectional growth outcomes were described by z scores for weight for age (WAZ) and height for age (HAZ) using the 2000 Centers for Disease Control and Prevention (CDC) sex-specific growth reference.\textsuperscript{14} Undernutrition was defined as 2 standard deviations (SDs) below zero and overweight was defined as 2 SDs above zero, according to World Health Organization criteria.\textsuperscript{15}

Fasting was defined as an overnight fast of 8 hours or more, and 134 participants satisfied this criterion and had complete perinatal and follow-up data.

Residence at the time of follow-up was defined as remote (residence in defined remote Aboriginal communities) or other (including the twin cities of Darwin and Palmerston and the greater Darwin area).

Statistical analysis

The clinical characteristics were summarised as means (SD), and if not normally distributed, as geometric means (SD) and as category percentages. Characteristics were compared between sexes using the t test (for normally distributed values) and the $\chi^2$ test (for categorical values). Non-normal data were transformed to normal distribution before $t$ tests were performed.

Representativeness of the fasting sample, as described above, was tested using $t$, Wilcoxon and $\chi^2$ tests, depending on the distribution of the test variable.

For analyses, birthweight, and adolescent height, weight and body mass index (BMI) were continuous variables, while birthweight for gestational age was dichotomised at the 10th percentile for FGR and at the 90th percentile for large for gestational age.

The relationships of fasting insulin, glucose and HOMA-IR measures to the birth size and current adolescent size were each analysed in standard regression models using the approach recommended by Lucas and colleagues\textsuperscript{16} adjusted for gestational age, sex, and contemporary age using Stata, version 11 (StataCorp).

In order to maintain the assumptions of regression-dependent variables, fasting insulin, glucose and HOMA-IR values were transformed using the natural log transformation. Each outcome variable was tested in separate univariate models for each of the birth measures (eg, model 1), then adjustment for height (eg, model 1a) or weight (eg, model 1b) was added to the model, then an interaction term between the birth measures and adolescent weight or height was added. Lastly, the outcome variables were tested in separate univariate models for adolescent height (eg, model 3) and weight (eg, model 4). Models were separately analysed with current-residence regression coefficients and were then back-transformed using exponentiation, presenting ratios for ease of interpretation.

The percentage of total variance in the outcome measures, accounted for by early life size and later adolescent size, were estimated by the difference in the coefficients of determination ($R^2$) between fully adjusted birth models with and without the measure of interest.

Ethics

The Human Research Ethics Committee of the Northern Territory Department of Health and Families and Menzies School of Health Research, including the Aboriginal Ethics Sub Committee, which has the power of veto, approved the study. Written consent was obtained in the form of an itemised consent with participants allowed to refuse individual procedures.

Results

One hundred and thirty-four participants had complete perinatal and follow-up data and fasting insulin and glucose measures. Box 1 shows the comparison of the fasting subset with the complete cohort and the subset of participants who did not have fasting values. This fasting subset was not significantly different from the non-fasting subset in the perinatal measures, the follow-up measures and the levels of non-fasting biomarkers (glycated haemoglobin and C-reactive protein) associated with type 2 diabetes. There were 59 males and 75 females with a mean age of 18.14 (SD, 1.1) years. The birth and adolescent characteristics of this fasting subset are shown in Box 2. As expected, females were significantly shorter ($P<0.01$) and lighter ($P<0.01$). Only one participant had a fasting glucose $>7$ mmol/L and there were no participants with fasting glucose values of 6.1–6.9 mmol/L.
For the fasting dataset, using the international CDC reference, the mean WAZ scores were negative for both males and females. The proportions of males and females with $WAZ < -2$ (undernutrition) were 18.6% and 17.3%, respectively. At follow-up, none of the 33 fasting adolescents who had been fetal growth restricted at birth had a $WAZ > 2$ (overweight/obesity). Only one participant had a $WAZ > 2$, with a similar profile occurring for those who had LBW.

Birthweight had a significant positively directed association with fasting glucose but not with fasting insulin levels. For every kg increment in birthweight, adolescent fasting glucose levels rose by 7% ($P = 0.002$) (Box 3). This positively directed association of birthweight with fasting glucose levels remained after adjustment for adolescent height or weight, which accounted for 6% and 3% of the variation in fasting glucose levels, respectively.

The significant association with fasting glucose levels also remained when birthweight was categorised as birthweight for gestational age. For adolescents who had been fetal growth restricted at birth, fasting glucose levels were 7% less than for those who were not fetal growth restricted at birth ($P = 0.003$), and these relationships remained the same after adjustment for adolescent height and weight, again accounting for 6% and 3% of the variation in fasting glucose levels (Box 3).

Current height, weight and BMI had significant and positively directed associations with both fasting insulin and glucose levels in univariate models, with the regression ratio and percentage of variation explained being greatest for the fasting adolescent insulin and HOMA-IR measures.

For every kg increment in weight, cm increment in height or index point in BMI, fasting insulin levels rose by 3%, 3% and 9%, respectively (Box 4), and HOMA-IR by 3% (95% CI, 1.02–1.04; $P < 0.001$), 3% (95% CI, 1.01–1.06; $P = 0.01$) and 10% (95% CI, 1.08–1.13), respectively (data for HOMA-IR not shown), while for fasting glucose, the changes were 0.1% increase for every kg increment in weight, 0.2% for every cm increment in height, and 0.7% for every index point in BMI (Box 3).

Repeat analysis of all models with the inclusion of the remote status variable did not change any of the associations previously found. Regression models (models 3, 4 and 5 in Box 3 and Box 4) of height, weight and BMI were also reanalysed, with adjustment for birthweight, which did not change the results presented.

Apart from these main effects, there were positive and significant interactions between birthweight and height for insulin ($P = 0.006$) and HOMA-IR ($P = 0.015$) (data not shown). This allows for an extra increment in insulin and HOMA-IR values for participants who moved from higher birthweight to higher adolescent height. Hence, for a fixed current height, those adolescents with higher birthweights had higher measures of insulin and HOMA-IR values.

**Discussion**

In this adolescent cohort, there were no negatively directed associations between birthweight and either fasting glucose, insulin concentrations or the insulin-resistance measure, with no evidence of the U-shaped associations described for populations with similar high rates of type 2 diabetes in adult life. A positively directed association occurred for birthweight with fasting glucose levels. Consistent with these findings, those adolescents who had been fetal growth restricted at birth had lower fasting glucose concentrations. In contrast, even in this young and lean population, there were positively directed associations of current adolescent height and weight with fasting glucose and insulin concentrations and the insulin-resistance measure, albeit of a relatively trivial magnitude for fasting glucose. For fasting glucose levels, the effect of birthweight and current weight was similar ($R^2 = 0.070$ v 0.076), but for fasting insulin levels, the effect of current weight was considerably stronger than birthweight ($R^2 = 0.299$ v 0.019). These overall findings are similar to findings for these Aboriginal cohort participants at 11 years of age.\(^\text{17}\)

The proportions of males and females with undernutrition ($WAZ < -2$) were 18.6% and 17.3%, respectively, which far exceeded the expected 2.3% using the CDC sex-specific growth ref-
ence.14 Hence, compared with this international reference, there was a marked excess of undernutrition in this cohort. Importantly, the findings of no associations between LBW and FGR with higher fasting adolescent insulin and glucose levels were contrary to the DOHaD hypothesis, and suggest that the adverse effects of poor fetal nutrition may be concealed by the persistent undernutrition in these Aboriginal adolescents.

The main strength of this study is that the data have been prospectively collected from a contemporary Australian Indigenous population. This is in contrast to many of the other studies examining the DOHaD hypothesis, which are retrospective studies.

Unusually for this type of cohort, at the time of recruitment less than 10% of mothers had homebirths.9 The single-point tertiary hospital recruitment meant birth measurements were standardised, and reliable gestational age estimations were all made by the one neonatal paediatrician within 4 days of birth. Hence, the better fetal growth surrogate of birthweight adjusted for gestational age was available for analysis. Further, all follow-up biological measures were directly collected.

The difficulty in obtaining reliable fasting blood samples in the field is reflected in the small sample size. However, a number of significant associations were present despite this sample size. A further limitation due to the age of participants is the necessity of using intermediary biomarkers of diabetes instead of the preferred specific disease end point. Further, all follow-up biological measures were directly collected. Similar findings to our study have been reported from Aboriginal populations19 and low- or middle-income-country birth cohorts.20

Given the high prevalence of overweight and obesity currently seen in the adult Aboriginal population,6 it is likely that the growth trajectory will positively change in this cohort and the high-risk combination of LBW- or FGR-associated later obesity or overweight.

4 Size at birth and adolescent height and weight: relationships with fasting glucose (mmol/L) concentrations among Aboriginal adolescents (n = 134)*

<table>
<thead>
<tr>
<th>Model 1: birthweight, kg</th>
<th>Ratio</th>
<th>95% CI</th>
<th>P</th>
<th>R²</th>
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<tr>
<td>Model 1a: adjusted for child height</td>
<td>1.07</td>
<td>1.03–1.11</td>
<td>0.002</td>
<td>0.070</td>
</tr>
<tr>
<td>Model 1b: adjusted for child weight</td>
<td>1.07</td>
<td>1.02–1.11</td>
<td>0.005</td>
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</tr>
<tr>
<td>Model 2: FGR‡ v non-FGR§</td>
<td>0.93</td>
<td>0.89–0.98</td>
<td>0.003</td>
<td>0.062</td>
</tr>
<tr>
<td>Model 2a: adjusted for child height</td>
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<td>0.006</td>
<td>0.055</td>
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<tr>
<td>Model 2b: adjusted for child weight</td>
<td>0.95</td>
<td>0.90–0.99</td>
<td>0.028</td>
<td>0.033</td>
</tr>
<tr>
<td>Model 3: current height, cm</td>
<td>1.002</td>
<td>0.99–1.01</td>
<td>0.179</td>
<td>0.013</td>
</tr>
<tr>
<td>Model 4: current weight, kg</td>
<td>1.001</td>
<td>1.001–1.003</td>
<td>0.001</td>
<td>0.076</td>
</tr>
<tr>
<td>Model 5: body mass index</td>
<td>1.007</td>
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FGR = fetal growth restriction. *All models adjusted for gestational age, sex and contemporary age. †Difference between fully adjusted birth models with and without the measure of interest. ‡Birthweight < 10th percentile for gestational age. §Birthweight > 10th percentile for gestational age.

5 Size at birth and adolescent height and weight: relationships with fasting insulin concentrations (mU/L) among Aboriginal adolescents (n = 134)*

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<td>Model 1a: adjusted for child height</td>
<td>1.28</td>
<td>0.94–1.73</td>
<td>0.112</td>
<td>0.019</td>
</tr>
<tr>
<td>Model 1b: adjusted for child weight</td>
<td>1.12</td>
<td>0.82–1.54</td>
<td>0.471</td>
<td>0.004</td>
</tr>
<tr>
<td>Model 2: FGR‡ v non-FGR§</td>
<td>0.87</td>
<td>0.66–1.15</td>
<td>0.326</td>
<td>0.005</td>
</tr>
<tr>
<td>Model 2a: adjusted for child height</td>
<td>0.92</td>
<td>0.65–1.31</td>
<td>0.656</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 2b: adjusted for child weight</td>
<td>1.01</td>
<td>0.71–1.43</td>
<td>0.961</td>
<td>0</td>
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<tr>
<td>Model 3: current height, cm</td>
<td>1.27</td>
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The growth outcomes in our study suggest that a major nutritional mismatch between fetal and adolescent life has not occurred. It is likely that the permanent changes in response to undernutrition in utero have remained appropriate in this undernourished adolescent population with low rates of the high-risk combination of LBW- or FGR-associated later obesity or overweight.

3 Size at birth and adolescent height and weight: relationships with fasting glucose (mmol/L) concentrations among Aboriginal adolescents (n = 134)*

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The difficulty in obtaining reliable fasting blood samples in the field is reflected in the small sample size. However, a number of significant associations were present despite this sample size. A further limitation due to the age of participants is the necessity of using intermediary biomarkers of diabetes instead of the preferred specific disease end point. Socioeconomic status (SES) factors are potential confounders in this study and standard SES indicators were collected, such as years of schooling, house ownership and employment. There are limitations of standard measures in capturing the multidimensional differences within populations similar to this cohort population.18 In the absence of adequate discriminatory measures of SES, we used only remote current residence as an objective surrogate measure of SES. Including this variable made only a limited difference to the significance of one association.

Our findings are in contrast to the predominant literature of the DOHaD hypothesis describing inverse associations between birthweight and later fasting insulin and glucose levels. While these reports are mainly retrospective studies from developed populations,1 similar findings have been reported from Aboriginal populations19 and five low- or middle-income-country birth cohorts.20

Further, in the Newcastle Thousand Families Study, at 49–51 years of age, adult lifestyle factors explained larger proportions of variances for fasting and 2-hour glucose compared with early-life measures.22,23 A contemporary study of British children, based on maternal recall of birthweight, reports current size as the main determinant of insulin and glucose concentrations in childhood.24

The main strength of this study is that the data have been prospectively collected from a contemporary Australian Indigenous population. This is in contrast to many of the other studies examining the DOHaD hypothesis, which are retrospective studies.
In the meantime, our findings suggest that the current high rates of type 2 diabetes observed in the adult Aboriginal population are more likely to be decreased by strategies targeted to improve lifestyle factors in childhood and adolescence, rather than those focusing on improving birthweight alone.

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