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SHORT COMMUNICATION

Offspring birthweight is not associated with paternal insulin resistance

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Abstract
Aims/hypothesis Low birthweight is associated with insulin resistance and other insulin resistance-related phenotypes: diabetes, hypertension, and vascular disease in later life. The underlying mechanism is unclear. The foetal insulin hypothesis proposes that a single genetic predisposition to beta cell dysfunction/insulin resistance results in both reduced insulin-dependent foetal growth in utero, hence low birthweight, and predisposition to type 2 diabetes. The aim of this study was to test whether, as predicted by the foetal insulin hypothesis, there is an association between measures of paternal insulin resistance and offspring birthweight.

Subjects and Methods The Exeter Family Study of Childhood Health (EFSOCH) is a community-based study within central Exeter (UK), established to test the foetal insulin hypothesis prospectively. Associations were tested between offspring birthweight and paternal insulin resistance, calculated by homeostasis model assessment analysis in 986 families using data relating to singleton, non-diabetic, UK white pregnancies. Ethics approval was given by the North and East Devon local ethics committee.
Results Offspring birthweight was not significantly correlated with log paternal insulin resistance (r=0, p=0.91), log HDL cholesterol concentration (r=−0.02, p=0.47) or log triglyceride concentration (r=0, p=0.99) when corrected for paternal BMI and common confounders. Multiple linear regression analysis confirmed that paternal insulin resistance was not an independent predictor of offspring birthweight.
Conclusions/interpretation Results from a young, adult, non-diabetic population do not support the foetal insulin hypothesis as an explanation for the association of low birthweight with insulin resistance.

Keywords Birthweight · Insulin resistance · Offspring · Paternal

Abbreviations
HOMA homeostasis model assessment

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Introduction

Low birthweight is associated with insulin resistance and related conditions, including type 2 diabetes, but the underlying mechanism is unclear [1]. The thrifty phenotype

hypothesis proposes that foetal malnutrition in utero results in reduced foetal growth and programming of the foetus to be insulin-resistant postnatally [2]. In contrast, the foetal insulin hypothesis proposes that low birthweight and type 2 diabetes are two phenotypes of a genetic predisposition to insulin resistance and/or beta cell dysfunction that reduces insulin-dependent foetal growth in utero as well as predisposing to type 2 diabetes [3].

We proposed that, if insulin resistance is in part genetically determined, a test of the foetal insulin hypothesis would be that offspring of insulin-resistant fathers, who will inherit 50% of paternal genes, should have reduced insulin-mediated growth in utero, and hence lower birthweight [3]. Therefore, the primary analysis in this study was to test whether paternal insulin resistance is inversely associated with offspring birthweight.

Subjects and methods

The Exeter Family Study of Childhood Health (EFSOCH) was established to test the foetal insulin hypothesis prospectively. Details of the study, recruitment, protocol and planned analysis have been described previously [4]. In brief, we recruited both parents from 1,017 singleton, non-diabetic pregnancies from central Exeter, UK. At 28 weeks of gestation we measured parental height, weight, BMI and waist/hip ratio, and measures of paternal and maternal insulin resistance (including homeostasis model assessment [HOMA] [5], fasting plasma:glucose ratio, and insulin, HDL cholesterol and triglyceride concentrations). Offspring weight, length, head circumference and skin-fold thickness were measured at birth. DNA from the mother, father and baby were analysed to confirm family relationships.

Associations were examined between measures of paternal insulin resistance and offspring birthweight, corrected for sex and gestation, using correlation and regression analysis. The models were adjusted for potential maternal confounders, including prepregnant BMI, smoking, fasting glucose, insulin resistance and parental height. Variable distributions were assessed for normality and were log-transformed when necessary.

Results

Characteristics of study group

Of the original 1,017 families recruited, 27 families were excluded before birth and a further four families were excluded after birth [4]. The characteristics of the parents and offspring of the remaining 986 families at 28 weeks of gestation are given in Table 1.

Paternal insulin resistance and offspring birthweight

There was no significant correlation between paternal log insulin resistance and offspring birthweight corrected for known confounding factors and paternal BMI (r=−0.01, p=0.74) (Table 2). Traits associated with paternal insulin resistance were not correlated with corrected birthweight (log HDL, r=−0.02, p=0.55; log triglyceride concentration, r=0, p=0.95). Excluding offspring born before 37 weeks of gestation (n=943) made no difference to the results.

Paternal insulin resistance and offspring birth parameters associated with insulin resistance

There were no significant correlations between paternal log insulin resistance and other measures of offspring growth: length (r=0.02, p=0.58); head circumference (r=0.01,

Table 1 Baseline characteristics of 986 families (offspring and their parents)

	Mean or geometric mean	SD range
Mothers		
Age (years)	30.4	25.2–35.6
Height (cm)	165.0	158.7–171.3
Prepregnant weight (kg)	63.1[a]	52.5–173.8
Prepregnant BMI (kg/m^2)	23.4[a]	19.9–27.5
Pregnant weight (kg)	75.8[a]	64.6–89.1
Fasting plasma glucose (mmol/l)	4.3	3.9–4.7
Fasting plasma insulin (pmol/l)	60.3[a]	20.9–173.8
Fathers		
Age	32.9	26.9–38.9
Height (cm)	178.0	171.4–184.6
Weight (kg)	83.2[a]	70.8–97.7
BMI (kg/m^2)	26.3[a]	22.9–30.2
Waist/hip ratio	0.9	0.8–1.0
Plasma HDL cholesterol (mmol/l)	1.3[a]	1.0–1.7
Triglycerides (mmol/l)	1.3[a]	0.77–2.24
Fasting plasma glucose (mmol/l)	4.7	4.3–5.1
Fasting plasma insulin (pmol/l)	54.9[a]	30.9–97.7
HOMA-IS	85.1[a]	49.0–147.9
Babies (491 males)		
Gestation (weeks)	40.1[b]	39.0–41.0
Length (cm)	50.2	48.1–52.3
Birthweight (g)	3462	2947–3977
Ponderal index (kg/m^3)	27.6	25.0–30.2

Parental fasting blood and parental anthropometric measures were determined at 28 weeks of gestation; offspring measures were determined within 24 h of birth

HOMA-IS homeostasis model assessment of insulin sensitivity

[a] Geometric mean and SD range; [b] median and interquartile range; other data are mean and SD range

Table 2 Relationship of offspring birthweight with paternal insulin resistance: correlations of paternal insulin resistance, and traits related to paternal insulin resistance, with offspring birthweight and offspring birthweight corrected for common confounders (gestational age, sex, maternal parity and socio-economic status [SES]) and paternal BMI

	Birthweight		Birthweight corrected for sex, gestational age, parity and SES		Birthweight corrected for sex, gestational age, parity, SES and paternal BMI	
	r	*p*	*r*	*p*	*r*	*p*
Full data set (*n*=986)						
Log paternal insulin resistance	0.02	0.62	0.01	0.79	−0.01	0.74
Log paternal HDL cholesterol concentration	−0.05	0.16	−0.03	0.34	−0.02	0.55
Log paternal triglyceride concentration	0	0.91	0.02	0.61	0	0.95
Term only data set (*n*=943)						
Log paternal insulin resistance	0.01	0.75	0.01	0.73	0	0.91
Log paternal HDL cholesterol concentration	−0.04	0.28	−0.03	0.32	−0.02	0.47
Log paternal triglyceride concentration	−0.01	0.80	0.01	0.69	0	0.99

p=0.80); sum of skin-fold thicknesses (*r*=−0.00, *p*=0.99); ponderal index (*r*=−0.04, *p*=0.20).

Multivariate analysis

Multiple linear regression analysis was undertaken to assess any independent relationship between parental insulin resistance and offspring birthweight when adjusting for potential confounders (Table 3). There was no relationship between parental insulin resistance and offspring birthweight. In our model, the strongest predictors of offspring birthweight were gestation, foetal sex, maternal parity, maternal smoking, maternal fasting plasma glucose, maternal prepregnancy BMI and parental heights.

Discussion

This prospective study did not confirm the prediction of the foetal insulin hypothesis, which proposes that offspring birthweight is inversely related to paternal insulin resistance. This is in contrast to a UK study of 2,788 men aged 60–78 years, which found a weak inverse relationship between paternal insulin resistance and offspring birthweight [6], and four studies that have shown that fathers with type 2 diabetes have offspring with reduced birthweight [6–9]. It appears that birthweight has a weaker inverse association with paternal insulin resistance than with paternal diabetes [6], so our study may have been underpowered. However, our study had sufficient power to detect a difference as small as 50 g. Our subjects were approximately half the age of the subjects in the study by Wannamethee and colleagues [6], which might be part of the explanation for the different results.

Table 3 Relationship of offspring birthweight with paternal insulin resistance: multiple linear regression analysis with offspring birthweight (g) as dependent variable (*n*=943)

	b	Lower 95% confidence limit	Upper 95% confidence limit	*t*	*p*
Sex (male)	125	71	178	4.6	<0.001
Gestation (weeks)	167	145	190	14.6	<0.001
Primiparous	−182	−236	−128	−6.6	<0.001
Maternal smoking	−238	−324	−153	−5.5	<0.001
Maternal fasting glucose	218	137	299	5.3	<0.001
Maternal prepregnant BMI	15	8	22	4.1	<0.001
Maternal height	15	10	19	6.5	<0.001
Paternal height	7	3	11	3.5	<0.001
Socio-economic status	6	−2	15	1.5	0.13
Paternal BMI	4	−4	12	0.9	0.35
Paternal log insulin resistance	−48	−177	81	−0.7	0.46
Maternal log insulin resistance	44	−133	201	0.5	0.58

b Regression coefficient; *t* *t*-statistic defined as *b*/standard error

It is unlikely that the failure of our study to see any association was due to methodological difficulties. Our study benefited from the availability of a large number of prospectively collected parental and offspring data which had been obtained using strict quality control measures. The availability of considerable information on the mothers allowed all known confounders to be corrected for in the analysis.

The foetal insulin hypothesis assumes that foetal insulin resistance would result in reduced insulin-mediated growth in utero. However, if there was foetal compensation for increased foetal insulin resistance, this could result in foetal hyperinsulinaemia, and hence foetal growth would be relatively maintained despite a reduced response to insulin by the foetal tissues. This has been demonstrated in Indian babies, who are smaller and more insulin-resistant compared with European white babies, yet show increased cord insulin values [10]. Further support for foetal compensation comes from the inverse association between paternal insulin resistance and cord insulin concentrations we have seen in this cohort [11].

The foetal insulin hypothesis is based on the inheritance of genes that alter not only insulin resistance but also insulin secretion. For pragmatic reasons, this study was designed to examine paternal insulin resistance using HOMA from fasting plasma glucose and insulin concentrations. We were unable to measure beta cell function effectively, as this would require measuring a stimulated response such as insulin secretion in response to an oral glucose load, which would have required considerable additional resources. It is possible that the clearly reduced birthweight of offspring of fathers with type 2 diabetes [6–9] reflects the inheritance of genetic susceptibility to beta cell dysfunction. One approach that could be used to study this in the future would be to use the DNA that is available from the families in our study and look at the impact on birthweight of polymorphisms that predispose to diabetes by reducing beta cell dysfunction.

In conclusion, we have found no relationship between offspring birthweight and paternal insulin resistance in a cohort of young, white, singleton, non-diabetic pregnancies. This result does not support the foetal insulin hypothesis as the explanation of the inverse association between birthweight and insulin resistance.

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