Paternal Metabolic and Cardiovascular Risk Factors for Fetal Growth Restriction

Sara Hillman, MRCoG
Donald M. Peebles, FRCoG
David J. Williams, FRCP

OBJECTIVE—Fathers of low–birth weight offspring are more likely to have type 2 diabetes and cardiovascular disease in later life. We investigated whether paternal insulin resistance and cardiovascular risk factors were evident at the time that fetal growth–restricted offspring were born.

RESEARCH DESIGN AND METHODS—We carried out a case-control study of men who fathered pregnancies affected by fetal growth restriction, in the absence of recognized fetal disease (n = 42), compared with men who fathered normal–birth weight offspring (n = 77). All mothers were healthy, nonsmoking, and similar in age, BMI, ethnicity, and parity. Within 4 weeks of offspring birth, all fathers had measures of insulin resistance (HOMA index), blood pressure, waist circumference, endothelial function (flow-mediated dilatation), lipid profile, weight, and smoking habit. Comparison was made using multivariable logistical regression analysis.

RESULTS—Fathers of fetal growth–restricted offspring [mean (SD) 1.8th (2.2) customized birth centile] were more likely to have insulin resistance, hypertension, central adiposity, and endothelial dysfunction and to smoke cigarettes compared with fathers of normal grown offspring. After multivariable analysis, paternal insulin resistance and smoking remained different between the groups. Compared with fathers of normal grown offspring, men who fathered pregnancies affected by fetal growth restriction had an OR 7.68 (95% CI 2.63–22.40; P < 0.0001) of having a 1-unit higher log HOMA-IR value and 3.39 (1.26–9.16; P = 0.016) of being a smoker.

CONCLUSIONS—Men who recently fathered growth-restricted offspring have preclinical evidence of the insulin resistance syndrome and are more likely to smoke than fathers of normal grown offspring. Paternal lifestyle may influence heritable factors important for fetal growth.

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The role of maternally inherited risk alleles for type 2 diabetes on fetal growth is difficult to assess owing to the confounding effect of maternal hyperglycemia on in utero environment (4). Support for the fetal insulin hypothesis has come from epidemiological studies that showed men who develop diabetes in later life were more likely to have fathered low–birth weight offspring (5–8). These fathers are also at increased risk of cardiovascular disease (9). Whether this latter observation is secondary to paternal diabetes or other risks shared by parents of low–birth weight offspring, such as smoking, is uncertain.

A study of nondiabetic families that specifically tested the fetal insulin hypothesis was unable to correlate paternal insulin resistance with offspring birth weight (10). Another study showed that men who fathered small-for-gestational-age infants were more likely to be obese and have larger waist circumferences but did not measure insulin resistance (11). We carried out a case-control study to investigate whether elements of the insulin resistance syndrome, including hyperinsulinemia, hyperglycemia, endothelial dysfunction, dyslipidemia, hypertension, and upper-body fat redistribution, could be observed in men at the time that they fathered growth-restricted offspring.

RESEARCH DESIGN AND METHODS—A case-control study was undertaken at University College London Hospital (UCLH) between September 2009 and May 2011. Ethics approval for the study was granted by the joint UCLH/UCL ethics committee (09/H0713/28). All participants gave informed consent.

Fetal growth restriction was defined as <10th customized centile (12). Nonpathological factors affecting birth weight are gestational age, maternal height, maternal weight at booking, parity, and ethnic group (12). We used customized centile software to generate a “customized” centile, which a particular weight has achieved in relation to expected birth weight (12). We included cases that were to have an induction of labor or delivery by cesarean section because of reduced fetal size. Two case subjects delivered after spontaneous labor after induction of labor was planned. These cases were included in the study.

Fetal growth restriction due to structural, infective, or chromosomal causes or multiple pregnancies was excluded. We also excluded fetal growth restriction due to maternal disease. Before the study started, we recorded the causes of fetal growth restriction among singleton pregnancies in our hospital. We found that 37.6% of pregnancies affected by fetal

From the Institute for Women’s Health, University College London, London, U.K.
Corresponding author: David J. Williams, dj williams@ucl.ac.uk.
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growth restriction were associated with maternal disease, 14.1% had fetal abnormalities, and 31.8% fulfilled our recruitment criteria. Data were unavailable for 16.5%.

Pregnant women and their partners thought to be having a normally grown baby were included if the estimated fetal weight was between the 10th and 95th customized centiles. We offered these participants an additional fetal ultrasound scan at 34 weeks to confirm predicted size.

A sample size calculation was made using STATA. Our initial calculation determined that 151 observations would be sufficient to detect a doubling in the odds ratio (OR) of a case having a unit increase in log homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) after adjustment for other covariables at 0.80 power and 0.05 significance. We were able to make 119 observations but calculated from the study data that we were powered at 0.96 to detect a doubling in the odds of a case having a unit increase in log HOMA insulin resistance compared with a control subject.

We recruited 44 couples with a pregnancy affected by fetal growth restriction (case subjects) and 85 couples with normally grown offspring (control subjects). After delivery, 8 families (2 case and 6 control subjects) were excluded, as neonatal measures did not match predicted fetal growth. Two further control subjects withdrew consent to study participation after delivery. Two families of case subjects were approached, but the fetus died before consent, after which time they declined to participate. Final study analysis was between 42 case and 77 control subjects.

In order to minimize differences in fetal growth caused by maternal in utero environment, we only selected pregnant mothers as case or control subjects if they were older than 18 years, conceived naturally, had a BMI between 20 and 35 kg/m², and did not have significant medical problems, take medications or recreational drugs, or smoke or drink alcohol during pregnancy. Women whose partner smoked had an additional antenatal test for cotinine (ABS Laboratories), a metabolite of nicotine, as an indicator of passive smoking.

All women and their partners who met inclusion criteria were approached while attending antenatal clinics or fetal ultrasound sessions. Some eligible participants responded to a research poster.

Each father completed a questionnaire inquiring about past medical, family, and treatment history. Own birth weight was recorded as remembered personally or from a parent. All study assessments were carried out in the Clinical Research Facility, UCLH. Men were studied within 4 weeks of offspring birth. The study room was temperature controlled at 24°C. Participants were asked to fast overnight for at least 10 h before study. Weight, height, and waist circumference (measured twice between the top of the iliac crests) were recorded. After resting, two measures of supine blood pressure were taken 15 min apart.

Fasting venous insulin, glucose, and lipid levels were measured. Insulin resistance was calculated using the HOMA model (13). We chose the HOMA model for its simplicity and correlation with more invasive tests of insulin resistance, such as glucose tolerance test (13) and euglycemic clamp (14). The blood was spun within 1 h of venepuncture, and plasma and serum were frozen at ~80°C. All blood samples were processed in the same laboratory.

Endothelial function was measured using brachial artery flow-mediated dilatation by a single operator (S.H.) in a quiet, temperature-controlled room in accordance with previously reported protocols (15). Each image recording was validated by a second operator unaware of the subjects’ group. This led to 22 (18.5%) scans being excluded from the final analysis owing to lack of agreement.

At the time of childbirth, umbilical cord blood was taken from the umbilical vein or artery, centrifuged, and stored at −80°C as plasma and serum for later measures of fetal insulin and C-peptide levels. Gestational length and offspring sex, weight, and length were recorded.

In order to assess how many fathers fulfilled a definition of the insulin resistance syndrome, we applied criteria of the European Group for the Study of Insulin Resistance (16). This definition includes nondiabetic individuals with the highest level (top 25%) of insulin resistance. Additional risk factors include 1) central obesity, waist circumference ≥94 cm; 2) dyslipidemia, triglycerides ≥2.0 mmol/L or HDL cholesterol <1.0 mmol/L or treated for dyslipidemia; 3) hypertension, blood pressure ≥140/90 mmHg; and 4) fasting plasma glucose at least 6.1 mmol/L.

### Statistical analysis

Statistical analysis was performed using the STATA 11 package with assistance from a UCL statistician. HOMA-IR was log² transformed to improve normality. All results are recorded as mean (SD) unless otherwise stated. Data were initially analyzed by univariable logistic regression. The sample size allowed us to use the four coefficients with the lowest P value to generate a multivariable model. The variables that remained significant were used to generate the final model. Sensitivity analysis using forward stepwise regression confirmed the validity of this approach. Maternal factors were forced into the final model and the results from the two models compared.

### RESULTS

Baseline characteristics of offspring confirmed that case and control subjects met the study criteria and that mothers of both case and control subjects had a similar phenotype (Table 1). Fathers of growth-restricted offspring (case subjects) had greater waist circumference and blood pressure and were more likely to smoke than fathers of normal grown offspring (Table 2). Fasting glucose and insulin levels were both higher in case subjects, which resulted in an elevated log HOMA-IR (Table 2). Cases also had lower measures of flow-mediated dilatation and tended to have a more atherogenic lipid profile (Table 2).

Initial univariable logistical regression analysis confirmed that paternal insulin resistance, blood pressure, and waist circumference were higher in case compared with control subjects, while flow-mediated dilatation was reduced and case fathers were more likely to smoke cigarettes (Table 3). The four most statistically significant paternal coefficients were log HOMA-IR, smoking, waist circumference, and diastolic blood pressure, which were analyzed in the multivariable analysis. Paternal insulin resistance and smoking remained different after multivariable analysis, and therefore the final model was run with these two variables (Table 3).

Compared with fathers of normal grown offspring, men who fathered pregnancies affected by fetal growth restriction had an OR 7.68 (95% CI 2.63–22.4, P < 0.0001) of having a 1-unit higher log HOMA-IR value and 3.39 (1.26–9.16, P = 0.016) of being a smoker (Table 3). With use of step-wise regression, no maternal variable affected these differences in paternal insulin resistance or smoking. In sensitivity analyses using forward stepwise regression and first including all paternal explanatory variables followed by additional maternal explanatory variables (maternal age and BMI), paternal
Table 1—Baseline maternal and offspring phenotype

|          | Case subjects | Control subjects |
|----------|---------------|------------------|
|          | Mean or n (%) | SD | 25th centile | 75th centile | Min | Max | Mean or n (%) | SD | 25th centile | 75th centile | Min | Max |
| Baby     |               |    |             |             |     |     |               |    |             |             |     |     |
| Customized birth centile (%) | 1.8 | 2.2 | 0.1 | 3.2 |     |     | 49.6 | 27.5 | 26 | 73.9 |     |     |
| Gestation (days) | 256 | 29 | 236 | 279 |     |     | 283 | 9.3 | 274 | 291 |     |     |
| Birth weight (g) | 2,019 | 752 | 1,378 | 2,650 |     |     | 3,517 | 367 | 3,290 | 3,800 |     |     |
| Mothers      |               |    |             |             |     |     |               |    |             |             |     |     |
| Age (years) | 33.8 | 4.52 | 25 | 44 |     |     | 32.3 | 3.57 | 20 | 39 |     |     |
| Weight (kg) | 62.7 | 9.2 | 48.4 | 84.1 |     |     | 64.4 | 10.5 | 44 | 94 |     |     |
| Height (cm) | 163 | 5.7 | 152 | 175 |     |     | 166 | 5.8 | 155 | 185 |     |     |
| Birth weight (g) | 3,007 (48) | 576 | 1,000 | 3,800 |     |     | 3,322 (58) | 425 | 2,300 | 4,300 |     |     |
| BMI (kg/m²) | 23.3 | 3.5 | 19 | 32 |     |     | 23.4 | 3.4 | 18 | 32 |     |     |
| Nulliparous | 31 (73.8) |     | 57 (74.0) |     |     |     |     |     |     |     |     |     |
| Multiparous | 11 (26.2) |     | 20 (26.0) |     |     |     |     |     |     |     |     |     |

Birth characteristics of offspring case subjects (<10th customized birth weight centile: n = 42) and control subjects (10th–90th customized birth weight centiles: n = 77). Customized birth centiles are gestation specific and detect fetal growth restriction despite reduced gestation. All mothers fulfilled baseline inclusion criteria, and maternal phenotype was similar between case and control subjects. Maternal own birth weight was available for 20/42 (48%) of cases and 45/77 (58%) controls. Max, maximum; Min, minimum.

smoking and insulin resistance were confirmed as the two significant variables.

With use of criteria for the insulin resistance syndrome defined by the European Group for the Study of Insulin Resistance in nondiabetic individuals (16), the majority of men in the highest quartile for insulin resistance (n = 30 of 119) were case subjects (19 of 42 case subjects [45%] compared with 11 of 77 control subjects [14%]) (Fig. 1). Most of these case subjects (10 of 19 [53%]) also had an increased waist circumference >94 cm, which was only noted in 2 of 11 (18%) control subjects (Fig. 1). We used this information to generate a second model limited to fathers in the top quartile for insulin resistance. After multivariable analysis, men in the top quartile for insulin resistance who fathered a growth-restricted fetus had an OR 6.72

Table 2—Baseline paternal phenotype

|          | Case subjects | Control subjects |
|----------|---------------|------------------|
|          | Mean or n (%) | SD | Min | Max | Mean or n (%) | SD | Min | Max | P |
| Age (years) | 34.8 | 5.71 | 23 | 47 | 33.3 | 4.69 | 22 | 50 | 0.158 |
| Weight (kg) | 83.4 | 11.8 | 57 | 106.9 | 80.2 | 10.2 | 55.2 | 112 | 0.13 |
| Height (cm) | 177 | 7.0 | 166 | 193 | 179 | 6 | 161 | 195 | 0.28 |
| Birth weight (g) | 3,127 (48) | 597 | 1,000 | 3,970 | 3,506 (48) | 380 | 2,780 | 4,540 | 0.005 |
| Waist circumference (cm) | 94.1 | 8.23 | 71 | 114 | 89.6 | 8 | 60.5 | 113 | 0.005 |
| BMI (kg/m²) | 26.2 | 3.25 | 18.7 | 31.5 | 25.2 | 2.93 | 16.8 | 32.2 | 0.08 |
| Systolic BP (mmHg) | 121.5 | 8.73 | 102 | 137 | 117.7 | 5.86 | 105 | 130 | 0.006 |
| Diastolic BP (mmHg) | 70.5 | 7.16 | 57 | 85 | 66.9 | 6.31 | 55 | 83 | 0.005 |
| Fasting glucose (mmol/L) | 4.87 | 0.41 | 4.2 | 6.4 | 4.72 | 0.32 | 3 | 5.4 | 0.037 |
| Fasting insulin (mIU/L) | 7.1 | 4.29 | 2 | 17.5 | 4.81 | 2.61 | 1.5 | 11 | 0.001 |
| Insulin resistance (HOMA) | 0.93 | 0.51 | 0.4 | 2.2 | 0.63 | 0.31 | 0.4 | 2 | <0.001 |
| Cholesterol (mmol/L) | 4.85 | 0.89 | 2.8 | 7.2 | 4.65 | 0.86 | 3.1 | 7.8 | 0.27 |
| Triglycerides (mmol/L) | 1.06 | 0.48 | 0.5 | 2.5 | 0.9 | 0.38 | 0.4 | 2.2 | 0.06 |
| HDL cholesterol (mmol/L) | 1.29 | 0.32 | 0.7 | 2.3 | 1.41 | 0.34 | 0.9 | 2.7 | 0.09 |
| LDL cholesterol (mmol/L) | 3.01 | 0.92 | 1.2 | 5.7 | 2.82 | 0.83 | 1.2 | 6.1 | 0.28 |
| FMD (%) | 6.45 | 3.5 | 1.15 | 15.6 | 8.12 | 3.08 | 3.65 | 17.17 | 0.017 |
| Smokers | 17 (40.5) | 15 (19.5) | 8 | 0.008 |

Paternal own birth weight was available for 20/42 (48%) cases and 37/77 (48%) controls. Baseline paternal phenotype showing that men who fathered growth-restricted offspring (case subjects) had a higher waist circumference and blood pressure and were more likely to smoke than fathers of normal grown offspring (control subjects). Metabolic features of case subjects included elevated fasting glucose and insulin levels with a more atherogenic lipid profile. Case subjects also had reduced flow-mediated dilatation (FMD) compared with control subjects. Comparison between groups using t test; P < 0.05 statistically significant. BP, blood pressure; Max, maximum; Min, minimum.
**Paternal phenotype and fetal growth restriction**

**Table 3—Logistical regression of paternal variables**

| Coefficients                  | Univariable analysis | Multivariable analysis |
|------------------------------|----------------------|------------------------|
|                              | OR       | 95% CI     | P         | OR       | 95% CI     | P         |
| Log insulin resistance (HOMA)| 5.99     | 2.25–15.91 | <0.0001  | 7.68     | 2.63–22.4 | <0.0001  |
| Smoker                       | 3.09     | 1.10–8.22  | 0.01     | 3.39     | 1.26–9.16 | 0.016    |
| Diastolic blood pressure (mmHg)| 1.09 | 1.02–1.16  | 0.006    |          |           |          |
| Systolic blood pressure (mmHg)| 1.08     | 1.02–1.14  | 0.007    |          |           |          |
| Waist circumference (cm)     | 1.08     | 1.02–1.14  | 0.007    |          |           |          |
| FMD (%)                      | 0.84     | 0.73–0.97  | 0.021    |          |           |          |
| BMI (kg/m²)                  | 1.12     | 0.99–1.28  | 0.081    |          |           |          |
| Weight (kg)                  | 1.03     | 0.99–1.07  | 0.133    |          |           |          |
| Age (years)                  | 1.06     | 0.98–1.14  | 0.158    |          |           |          |

The bold text indicates that after multivariable analysis, Log insulin resistance (HOMA) and smoking were significantly different between paternal cases and controls and therefore these 2 variables were run in the final statistical model. Compared with fathers of normal grown offspring, men who fathered pregnancies affected by fetal growth restriction had an OR 7.68 (95% CI 2.63–22.4; P < 0.0001) of having a 1-unit higher log HOMA-IR value and 3.39 (1.26–9.16; P = 0.016) of being a smoker. FMD, flow-mediated dilatation.

(95% CI 2.43–18.58; P < 0.0001) of having further risk factors for the insulin resistance syndrome and 3.36 (1.28–8.28; P < 0.013) of being a smoker compared with fathers of normal grown offspring.

Umbilical cord blood from fetal growth–restricted offspring (n = 10) and normal grown offspring (n = 20) had similar insulin levels [5.89 (7.6) and 5.40 (3.5) mIU/L, respectively, P = 0.81] and similar C-peptide levels [1.02 (0.75) and 1.06 (0.42) ug/L, P = 0.9]. There was no correlation between fetal cord blood insulin and paternal insulin levels.

Parental birth weight was known in 57 (48%) fathers and 65 (55%) mothers. Case fathers were lighter than control fathers [birth weight 3,127 (597) vs. 3,506 (380) g, respectively, P = 0.0045]. Case mothers were lighter than control mothers [birth weight 3,007 (576) vs. 3,322 (425) g, P = 0.012].

Maternal random glucose levels were similar during pregnancy [case subjects 4.45 (0.52) mmol/L and control subjects 4.54 (0.54) mmol/L, P = 0.4] and remained similar postpartum [case subjects 4.53 (0.37) mmol/L and control subjects 4.57 (0.46) mmol/L, P = 0.78]. Postpartum, maternal insulin levels were also similar between case [4.38 (2.41) mIU/L] and control [3.97 (2.15) mIU/L] subjects; P = 0.57. Postnatal maternal HOMA index was similar between case [0.58 (0.29)] and control [0.56 (0.24)] subjects; P = 0.57.

Only 3 women (2 case and 1 control) of a sample of 17 who had a partner who smoked had detectable serum cotinine levels. These levels were compatible with passive smoking (15.7, 45.9, and 59.3 ng/mL).

**CONCLUSIONS**—This case-control study identified women with pregnancies affected by fetal growth restriction and showed that their partners were more insulin resistant and more likely to smoke compared with fathers of normal grown offspring. Fathers of growth-restricted offspring also had other elements of the insulin resistance syndrome, including high blood pressure, endothelial dysfunction, upper–body fat redistribution, and a more atherogenic lipid profile. These observations support epidemiological studies that have consistently observed an increased incidence of type 2 diabetes and cardiovascular disease among men who previously fathered low–birth weight offspring (5–9).

Although our study provides objective evidence of subclinical insulin resistance at the time of fathering growth-restricted offspring, the Exeter Family Study of Childhood Health (EFSOCH), which studied almost 1,000 normal grown offspring and their fathers, did not find an association between offspring birth weight and paternal insulin resistance (10). Unlike our study, the EFSOCH study only investigated offspring with a normal birth weight (2.95–3.98 kg). Under these circumstances, paternally inherited insulin resistance may be compensated by increases in fetal insulin production. This suggestion was supported by their observation that paternal insulin resistance was inversely correlated with fetal insulin concentrations (17). In a subset of our...
study population, we were unable to detect such a relationship between paternal insulin resistance and fetal cord blood insulin or C-peptide levels. It is possible that our secondary analysis did not have statistical power to detect such a correlation. Another explanation is that our study case subjects may have included a mixture of growth-restricted offspring, some with insulin resistance and high fetal insulin levels and others with reduced β-cell function and low fetal insulin secretion, so that we were unable to detect a clear difference in overall insulin levels between case and control subjects. It is possible that other heritable factors that are passed from father to offspring influence both paternal phenotype and fetal growth.

We also showed that men who fathered growth-restricted offspring were themselves smaller at birth. This observation could be explained by either the inheritance of genes that limit fetal growth, such as is described in the fetal insulin hypothesis, or fetal adaptations in response to relative malnutrition in utero (the thrifty phenotype [18]). Fetal growth restriction is associated with an increased risk of perinatal death (19). It is also possible that survivors of fetal growth restriction, like all the case subjects in our study, have inherited paternal characteristics that predispose to weight gain and cardiovascular risk factors. During our study, two cases of fetal growth restriction resulted in intrauterine death, but the families were unwilling to participate in the study. Whether families of fetal growth–restricted offspring that result in perinatal death are different from families of survivors remains a challenging question to answer.

In our case-control study, we minimized the effect of maternal environment by only including healthy pregnant women within prespecified phenotypic limits and excluding fetal growth restriction due to recognized maternal or fetal diseases. This allowed us to study pregnancies predominantly affected by placental disease. These predetermined maternal inclusion criteria are likely to have strengthened the effects of paternally inherited factors. Others have found that men who father small-for-gestational-age offspring are more likely to be overweight and to have a greater waist circumference than fathers of normal grown offspring (11). Our study adds objective measures of paternal insulin resistance, endothelial function, and lipid profile to these phenotypic characteristics.

In our study, differences in blood pressure and endothelial function between the groups were no longer evident after adjustment for paternal smoking. Cigarette smoking is known to independently raise blood pressure and impair flow-mediated dilatation (20). Maternal smoking is a recognized risk factor for fetal growth restriction (21). We therefore excluded women who smoked from our study. However, the partners of some women smoked during pregnancy. Paternal smoking has previously been associated with fetal growth restriction and correlates with levels of maternal cotinine (22). In our study, maternal cotinine was only detectable in serum of 3 of 17 women whose partner smoked, compatible with low-level passive smoking. Although we did not check fetal cotinine levels from umbilical cord blood, it is unlikely that maternal passive smoking contributed to fetal growth restriction in our study. Maternal smoking can cause epigenetic change to human placental genes (22). It is currently unknown whether paternal smoking can cause epigenetic change that is inherited by the fetus and placenta.

For pragmatic reasons, we measured insulin resistance using the HOMA model derived from fasting insulin and glucose. A more robust but invasive technique is the euglycemic insulin clamp (14). HOMA correlates well with clamp-derived methods (14) and in our study is supported by other parameters associated with the insulin resistance syndrome.

Only four fathers of growth–restricted pregnancies (9.5% of cases) fulfilled a European definition of the insulin resistance syndrome (16). However, the majority of cases in the top 25% for insulin resistance also had central obesity as defined by a waist circumference >94 cm. Insulin resistance is closely linked with central obesity, which in turn precedes other elements of the metabolic syndrome (23). Subclinical insulin resistance at the time of fathering growth–restricted offspring not only explains the association with future paternal type 2 diabetes and cardiovascular disease but also identifies a group of men with a reversible risk factor for future metabolic and vascular disease (24), just as gestational diabetes mellitus identifies women at risk for future diabetes (25).

In men with established type 2 diabetes, a log unit increase in HOMA-IR has been associated with a 31% increased risk of cardiovascular disease (26). Insulin resistance in men without diabetes is an independent risk factor for future cardiovascular disease (27,28). Dietary and lifestyle measures can reverse insulin resistance and reduce future cardiovascular risk (29,30). Our observations, at the time of fathering a growth–restricted offspring, suggest that these men may benefit from advice on a healthy lifestyle as part of primary prevention of diabetes and cardiovascular disease.

Inheritance of common insulin control genes (31), rarer monogenic disorders of glucose metabolism (2), or other as yet unidentified heritable factors may explain our observed link between paternal insulin resistance and fathering growth–restricted offspring. It is possible that paternal lifestyle leading to obesity and smoking may drive epigenetic change that leads to insulin resistance, which is inherited by offspring and manifests as fetal growth restriction (32). This latter possibility requires further investigation.

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S.H. contributed to the study conception and design, analysis and interpretation of data, and revision of the manuscript. D.M.P. contributed to study design and revision of the manuscript. D.J.W. conceived the project idea and contributed to study design, interpretation of data, and writing of the manuscript. D.J.W. is the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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