Type 2 Diabetes and Low Birth Weight
The Role of Paternal Inheritance in the Association of Low Birth Weight and Diabetes

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Lower birth weight is associated with an increased occurrence of type 2 diabetes in later life. Whether this relationship is explained by environmental or genetic factors is unknown. We have examined the potential for genetic influences by determining whether parental diabetes is associated with lower birth weight in 1,608 children of known birth weight and gestational age born between 1941 and 1993 in the Gila River Indian Community in Arizona. The previously described relationships of maternal diabetes to increased birth weight and offspring diabetes were observed. In contrast to this we have determined novel relationships between low birth weight and paternal diabetes. The offspring of diabetic fathers were, on average, 78 g lighter than the offspring of nondiabetic fathers. For fathers, lower birth weight in their offspring was associated with an increased risk of later diabetes, i.e., fathers of offspring in the lowest quintile of birth weight, who were not diabetic at the time of birth of their child, had a 1.8-fold increased risk of developing diabetes later in life (95% CI 1.2–2.7; P = 0.004). For children, lower birth weight predicted diabetes in the offspring if paternal but not maternal diabetes was present, but it was not associated with higher plasma glucose if neither parent had diabetes. We conclude that the risk of diabetes associated with low birth weight is strongly related to the development of paternal diabetes, suggesting a genetic link between lower birth weight and later diabetes. *Diabetes* 49:445–449, 2000

Recent studies have demonstrated a relationship of lower birth weight to subsequent lifetime risk of developing diabetes, leading to the hypothesis that the environment in utero and, in particular, maternal undernutrition may program later risk of diabetes (1). An alternative hypothesis is that genes, e.g., acting to reduce insulin secretion or increase insulin resistance, independently predispose to diabetes and low birth weight and thus explain the observed epidemiological association (2).

Since 1965, members of the Gila River Indian Community have participated in a community-wide survey of diabetes and its complications. Members of the community over the age of 5 years are invited to participate in research examinations, including a biennial oral glucose tolerance test (OGTT) after a 75-g glucose load. In this population, both low and high birth weights are associated with later type 2 diabetes (3), the effects of high birth weight being mediated, at least in part, by the environment supplied to the fetus by the diabetic mother (4). The long-term epidemiological study in the Pima Indian Community has extensive data on the occurrence of diabetes in children and their parents. We hypothesized that if the association between low birth weight and later diabetes is due to genetic effects, then the parents of low birth weight offspring should themselves be at a greater risk of diabetes. Further, parental diabetes might also be associated with reduced birth weight, which, given the relationship of maternal diabetes to increased birth weight, would be expressed only in the offspring of diabetic fathers and nondiabetic mothers. Conversely, the absence of such effects would strengthen the case for early environmental influences being a cause of diabetes in these lower birth weight offspring.

RESEARCH DESIGN AND METHODS

Subjects. The 1,608 subjects of this report are at least half Pima or Tohono O'odham or a mixture of these two closely related groups. All those selected had a record of birth weight, a record of known length of gestation at delivery (also restricted to between 34 and 42 weeks), and OGTT data available from both parents. When parents had been tested on multiple occasions, the last available OGTT was used. When available (in 62% of parents), the result of the last OGTT carried out before the birth of their child was also analyzed separately. Diabetes was diagnosed if fasting blood glucose was ≥140 mg/dl, or glucose 2 h after the 75-g glucose load was ≥200 mg/dl, or if diabetes had been diagnosed in a clinical setting.

Statistical analyses. All data were analyzed in SAS (SAS Institute, Cary, NC). Corrected birth weight was derived by linear regression of actual birth weight against sex and gestational age. The residual value was then added to the estimated mean birth weight at 40 weeks to adjust individual birth weights to 40 weeks of gestation and male sex. Corrected birth weight was analyzed to allow for effects due to variation in gestational age at the time of delivery.

Age- and sex-adjusted diabetes prevalence in birth weight quintiles was calculated by the direct method using the age distribution of the 1,460 subjects with follow-up OGTT data as the reference population (Fig. 3).

As part of this analysis, the child's outcome was compared with a diabetes score derived for each parent in the sample (5). In brief, the diabetes score was derived by first calculating the sex-specific cumulative incidence of diabetes as a function of age (CI_a) in the Pima population. If diabetes was present, then the score is calculated by $1 - CI_a$ at the age of first diagnosis of diabetes. If diabetes was not present, then the score is calculated as $-CI_a$ at the time of the last examination. The

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BEFORE, oral glucose tolerance test on parent before the index pregnancy; LAST, last available oral glucose tolerance test on parent; MODY, maturity-onset diabetes of the young; OGTT, oral glucose tolerance test.

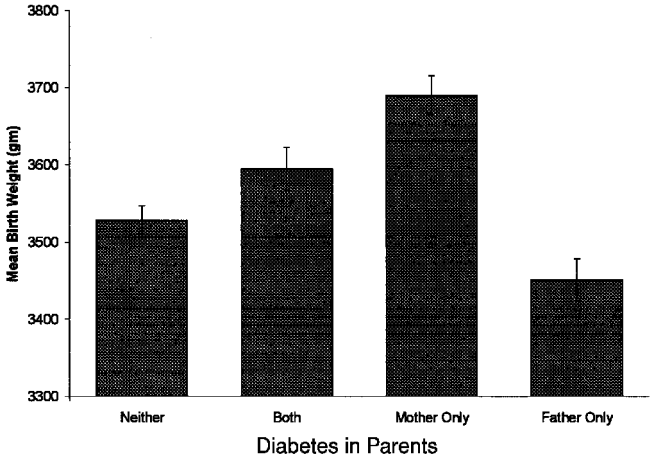

FIG. 1. Birth weight and parental diagnosis. Mean birth weight of children divided by last known diabetes status of their parent. Groups: Neither, neither parent ever diagnosed with diabetes; Both, both parents diagnosed with diabetes; Mother Only, mother diagnosed with diabetes, father nondiabetic; Father Only, father diagnosed with diabetes, mother nondiabetic. Values are expressed as means ± SE. General linear model consistent with a significant effect of parental diabetes diagnosis on birth weight ($P < 0.001$) and independent effects of both maternal (post hoc Student-Newman-Keuls test: $P < 0.0001$) and paternal (Student-Newman-Keuls test: $P < 0.001$) diabetes status.

score thus contains information on whether an individual developed diabetes and the age at onset of diabetes, being positive if diabetes was ever present and greater if diabetes developed at an earlier age. Conversely, a negative score is calculated if the individual was nondiabetic at the last examination and is most negative in those who remain nondiabetic into old age.

RESULTS

The association of parental diabetes and birth weight of their children. Birth weights were available for 1,608 individuals who had a mean gestational age of 39.7 ± 1.2 weeks and a mean corrected birth weight of 3,573 ± 488 g (mean ± SD). By design, OGTT data were available from all parents. The mean age at last examination of parents was 40.6 ± 14.5 years for fathers and 42.9 ± 12.8 years for mothers, with 41% of fathers and 50% of mothers having been diagnosed with diabetes.

Mean birth weight was related to the presence or absence of parental diabetes at the latest examination (Fig. 1: overall difference between groups, $P < 0.0001$). Maternal diabetes was positively ($P < 0.0001$) and paternal diabetes negatively ($P < 0.001$) associated with birth weight, with no significant interaction between them. Birth weight was highest when only the mother had developed diabetes and lowest when only the father had developed diabetes.

To further assess the relationship of parental diabetes to the birth weight of their children, the prevalence of parental diabetes was examined across quintiles of birth weight. Parental diabetes was examined separately in the subgroup in which OGTT data were available before the index pregnancy (BEFORE) and for all parents at their last available OGTT (LAST). Analysis of maternal diabetes by the birth weight quintile showed the expected positive relationship of maternal diabetes to birth weight. An excess of maternal diabetes of 7% was present in the highest quintile of birth weight both before the index pregnancy and at the mother's last examination (Fig. 2: BEFORE: $P < 0.001$; LAST: $P < 0.001$). Similar analysis for fathers revealed little relationship of birth weight

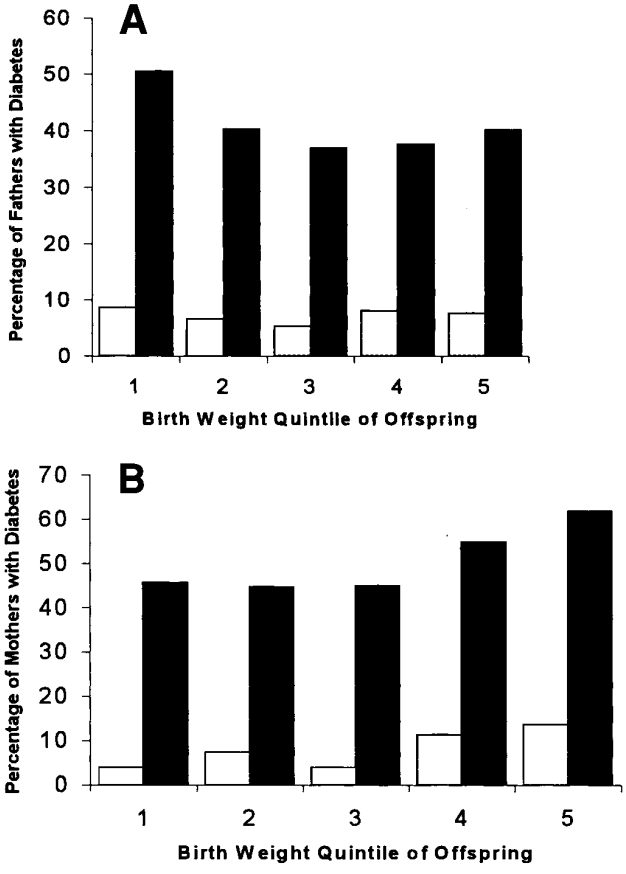

FIG. 2. Percentage of mothers and fathers with diabetes in comparison to birth weight quintile of their offspring. Quintiles: 1, lowest birth weight (mean ± SD: 2,944 ± 191 g); 5, highest birth weight (mean ± SD: 4,278 ± 366 g). *A*: Fathers: LAST data were available on fathers of all 1,608 offspring and BEFORE data for 58.5% ($n = 940$). □, BEFORE: test for trend not significant. ■, LAST: test for trend $P < 0.01$. *B*: Mothers: LAST data were available on mothers of all 1,608 offspring and BEFORE data for 65.7% ($n = 1,056$). □, BEFORE: test for trend $P < 0.001$; ■, LAST: test for trend $P < 0.001$.

to the father's diagnosis before the birth of the child, but lower birth weight was associated with a higher prevalence of paternal diabetes at the father's last examination (Fig. 2: BEFORE: $P = 0.9$; LAST: $P < 0.008$). There was an excess of paternal diabetes of 10% in the lowest birth weight quintile over all other quintiles.

These analyses, while suggesting a relationship between an eventual diagnosis of diabetes in fathers and lower birth weight in their children, do not account for potential confounding factors, such as the age at examination of parents and temporal trends in birth weight and diabetes diagnosis of children. To allow for these variables, the diabetes scores of parents (see RESEARCHDESIGNANDMETHODS) were compared with the birth weights of their children (for a parent with more than one child, the mean corrected birth weight of all available children was used). Linear regression was performed with mean birth weight as the dependent variable against the diabetes scores of mother and father. Calendar date of birth of parents (to allow for secular trends in diabetes incidence) and calendar date of birth of child (to allow for secular trends in birth weight) were included in each model as predictor variables. There was a positive relation-

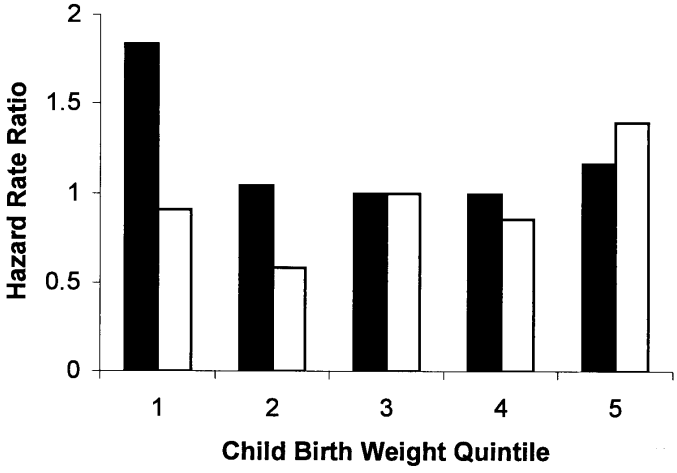

FIG. 3. Hazard rate ratio (mean and 95% CI) for later diabetes in parents who did not have diabetes at the time of birth of their children. Rates are compared with the middle quintile (which is set to 1). Overall birth weight quintile acted as a significant predictor of later paternal diabetes (likelihood ratio test: $P < 0.005$). ■, Father; □, mother.

ship of mother's diabetes score to the mean birth weight of her children ($n = 885$, $P < 0.0001$). For fathers the situation was reversed, with a significant negative relationship between father's diabetes score and the mean birth weight of his children ($n = 863$, $P < 0.03$). Thus, diagnosis of diabetes in the father was associated with lower birth weight in his children.

Birth weight and later diabetes in fathers. In fathers who did not have diabetes at the birth of their child, proportional hazards regression was performed, comparing risk of later paternal diabetes against the birth weight quintile of the mean birth weight of their children. Paternal age at the birth of the child and year of birth of father and last child were included in the regression model. The birth weight quintile of their offspring was a significant risk factor for later paternal diabetes ($P = 0.004$), with fathers of offspring in the lowest quintile of birth weight showing a 1.8-fold increased risk of developing diabetes later in life compared with those in the middle quintile (95% CI 1.2–2.7) (Fig. 3). Later diabetes was not similarly increased in mothers in the lowest quintile (hazard rate ratio 0.91, 0.56–1.46).

Diabetes in fathers and relative diabetes risk in their children. Of 1,608 offspring, 1,460 (91%) had been tested with an OGTT at an age at last examination of 19.5 ± 9.2 years (mean ± SD), and 165 (11.3%) had developed diabetes.

If paternal diabetes is associated with offspring diabetes by transmission of genes predisposing both to diabetes and low birth weight, then we hypothesized that paternal diabetes should be a stronger predictor of diabetes in offspring in lower birth weight groups than in higher birth weight groups. Thus, we modeled the relationship of maternal and paternal diabetes to diabetes risk in their offspring. Offspring were divided into tertiles of birth weight, and their propensity to diabetes was assessed by logistic regression. Diabetes in the offspring was entered into a model as the dependent variable, with mother's diabetes score, father's diabetes score, age of the child at examination, calendar date of birth, and sex of the child as the predictor variables, entered independently for each tertile. Maternal diabetes

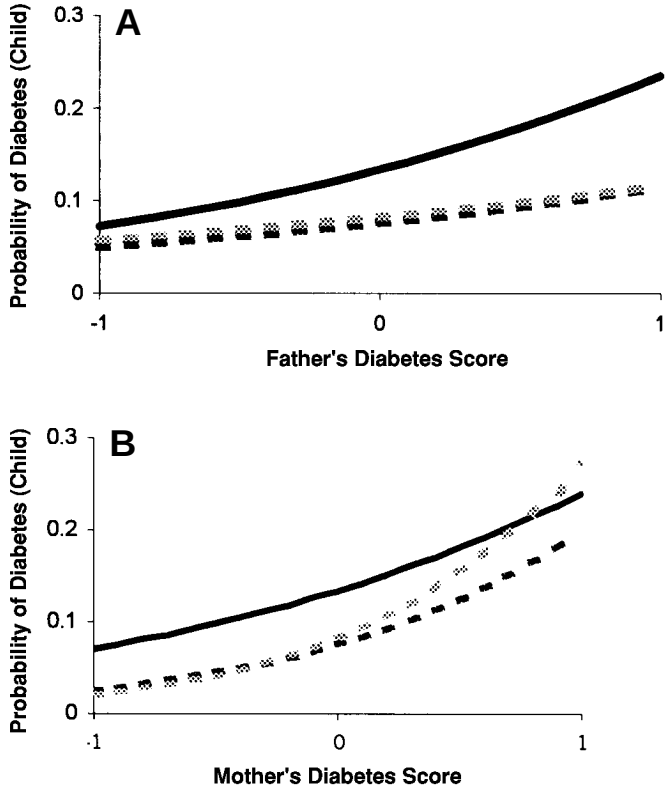

FIG. 4. Model parameter estimates for mother's and father's diabetes scores in predicting child diabetes outcome in logistic regression. Lowest (——), middle (– –), and highest (– –) tertiles of birth weight are shown. Other regression variables set to age 30 years, date of birth January 1, 1980, and male sex. A positive diabetes score indicates the diagnosis of diabetes, and higher scores indicate diagnosis at earlier ages. *A*: Father: the parameters above plus mother's diabetes score set to 0. Father's diabetes acted as a significant predictor of offspring diabetes only in the lowest tertile (parameter estimate 0.69: $P < 0.04$). *B*: Mother: the parameters above plus father's diabetes score set to 0. Mother's diabetes acted as a significant predictor of offspring diabetes in each tertile, with increasing effects as birth weight increased (lowest tertile parameter estimate: 0.72, $P < 0.02$; middle tertile parameter estimate: 1.1, $P < 0.003$; highest tertile parameter estimate: 1.4, $P < 0.001$).

was a significant predictor of offspring diabetes in each tertile, with increasing effects as birth weight increased. By contrast, the effect of paternal diabetes in predicting offspring diabetes was most marked, and only significant, in the lowest birth weight tertile (Fig. 4).

Birth weight and glucose tolerance in the offspring of nondiabetic parents. If birth weight and abnormalities of offspring glucose tolerance are due to influences in the intrauterine environment rather than the inheritance of parental genes predisposing to diabetes, then the relationship of low birth weight to offspring glucose tolerance should be present even in the offspring of nondiabetic parents. Among 157 offspring whose parents were known to be nondiabetic at their latest examination, and in whom the last parental examination had taken place at >35 years of age, 2-h postload plasma glucose, adjusted for age, sex, and birth year by linear regression, was examined in quintiles of birth weight. No significant difference in mean 2-h glucose concentration was seen, with only those in the highest birth weight group showing a trend toward higher glucose levels (Fig. 5).

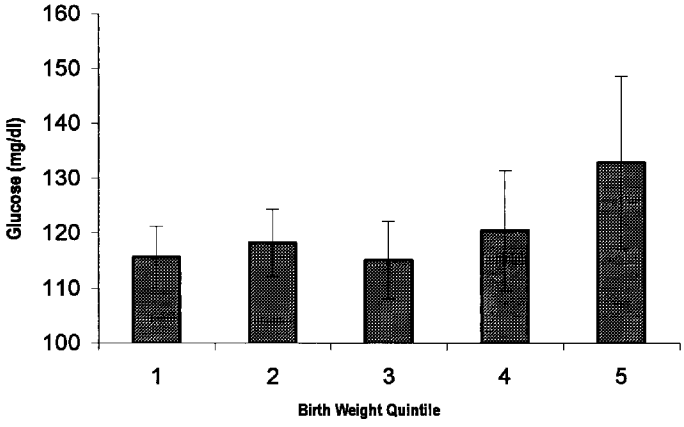

FIG. 5. The 2-h glucose in the offspring of nondiabetic parents and corrected glucose in birth weight quintiles. Glucose was corrected by multiple regression of glucose against sex, age, and birth date. Calculation of corrected values was made by addition of residuals of this equation to a reference value for age 30, date of birth January 1, 1980, and male sex. Quintiles were arranged from lowest (1) to highest (5). Quintile 1: n = 22; quintile 2: n = 30; quintile 3: n = 50; quintile 4: n = 31; quintile 5: n = 24. Analysis of variance revealed no differences between groups (F = 0.53, P = 0.71).

DISCUSSION

The observation that lower birth weight is associated with an increased diabetes risk has been confirmed in several populations and has prompted a variety of explanations. Alternative hypotheses invoke either genetic or environmental factors to explain the observed relationship, with lower birth weight being either an early phenotypic expression of a diabetes-prone genotype (2), or the result of an environmental insult that also predisposes to later diabetes (1), or reflecting a survival advantage of genes conferring insulin resistance to offspring of lower birth weight (3).

Some role for environmental effects is supported by the observations that lower birth weight is a risk factor for diabetes in identical twins discordant for diabetes (6). The low birth weight hypothesis of Barker et al. (1) proposes *1*) that the relation of low birth weight to diabetes risk is mainly explained by environmental factors, and *2*) that these factors mainly act in a specific time window during very early life. We have observed that fathers of low birth weight offspring have an increased lifetime risk of diabetes, as do their offspring. This would be consistent with the above argument only if father and child both experienced a similar environmental insult in early life. For this to be the case there would need to be a strong association of intrauterine or early life environment of father and child over time. This seems unlikely. Alternatively, the association of diabetes in lower birth weight child and father may be due to shared environmental precipitants to diabetes later in life, or because of shared genes. If diabetes risk in child and father were linked to environmental effects acting in later life, it is difficult to conceive a causative role of low birth weight in the later diabetes, as is proposed in the low birth weight hypothesis. In this model, the link between low birth weight and diabetes would simply arise as an epiphenomenon. Indeed, Barker et al. (1) have argued against such an interpretation on the basis that the association of low birth weight and later disease appears to be independent of factors affecting the adult environment, such as social class. Furthermore, the absence of an effect of low birth weight on 2-h glucose in the offspring of nondiabetic parents in our study argues against such an environmental model.

The most parsimonious explanation for the relationship between low birth weight and diabetes in offspring and parents is that genes predisposing to diabetes lead to lower birth weight. Insulin acts as a growth promoter in utero, and genes conferring either insulin resistance or a decrease in insulin secretion would therefore be well placed to lead to a decrease in fetal growth. Evidence for such mechanisms comes from Hattersley et al. (2), who have shown that the mutation in glucokinase that results in maturity-onset diabetes of the young (MODY)-2 and reduced insulin secretion is also associated with lower birth weight. Nevertheless, the low prevalence of the specific mutation causing MODY2, or other forms of MODY, means that these specific gene defects are highly unlikely to explain the association of low birth weight and diabetes seen across many populations.

Other genes involved in insulin action may influence birth weight. Two genes associated with raised fasting insulin levels in adult life have recently been associated with changes in birth weight (7,8). A common allelic variation in the insulin gene (*INS* VNTR) is associated with higher birth weight (7) and an increase in diabetes (9), while a variation in mitochondrial DNA (at bp 16189) is related to lower ponderal index (weight/height^3) and diabetes (8). For *INS* VNTR, an association with birth weight was significant only in offspring who did not change their rank in weight after birth (7), whereas the mitochondrial variant was significant only when restricted to those who had changed weight rank after birth (8).

Our observations differ from the model of Hattersley et al. (2) in that only paternal diabetes appears to be associated with lower birth weight. The Pima population has a high prevalence of diabetes and a high rate of maternal diabetes. Diabetes present during gestation leads to increased birth weight as a direct effect of hyperglycemia, and any effect of maternal diabetes genes to lower birth weight may therefore be obscured. If so, then in populations where mothers develop diabetes at a later age, such as those described by Barker et al. (1), lower birth weight of their offspring might be apparent. Alternatively, the possibility remains that the associations of lower birth weight and diabetes are explained by specifically paternal effects. Paternal diabetes increases the risk of offspring diabetes, and genetic imprinting would explain differential effects between father and mother. Imprinting appears to be more common in genes involved in fetal growth (10), and imprinted genes have also been implicated in the rare condition of transient neonatal diabetes. This condition is characterized by diabetes, present in the first few weeks of life, and low birth weight. It has been associated in ~20% of cases with paternal uniparental disomy of chromosome 6, leading to the suggestion that an imprinted gene in the 6q22–23 region of this chromosome might be the cause of the condition (11).

Current models of the etiology of type 2 diabetes invoke multiple genes and environmental influences, and low birth weight has been suggested as an important indicator of early environmental links with diabetes. Our results suggest that the association between low birth weight and type 2 diabetes may arise secondary to the transmission of genes promoting both low birth weight and susceptibility to diabetes.

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