Parental Transmission of Type 2 Diabetes
The Framingham Offspring Study

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Study of parental transmission of diabetes provides insight into the relative contributions of underlying maternal and paternal influences. We estimated risk for type 2 diabetes and milder degrees of glucose intolerance associated with parental diabetes among subjects of the population-based Framingham Offspring Study, in which participants are primarily Caucasian and at relatively low risk for diabetes and for which both parental and offspring phenotypes were ascertained by direct examination. Parental diabetes, assessed over 40 years of biennial follow-up, was defined by use of hypoglycemic drug therapy or a casual plasma glucose level ≥11.1 mmol/l at any examination. Offspring glucose tolerance, assessed over 20 years of quadrennial follow-up, was defined by fasting plasma glucose levels ≥7.8 mmol/l at any two examinations, use of hypoglycemic drug therapy at any examination, or with a 75-g oral glucose tolerance test (1980 World Health Organization criteria) at the most recent examination. We calculated odds ratios (ORs) and 95% CIs for offspring glucose tolerance status using generalized estimating equations to account for differential correlations within and between families. The 2,527 offspring came from 1,303 nuclear families, of which 77.6% had two or more siblings per family and in which the prevalence of parental diabetes was 24.6%. The mean offspring age was 54 years (range 26–82), 53% were women, 8.6% had diabetes, 11.4% had impaired glucose tolerance, 76.3% had no parental diabetes, 10.5% had maternal diabetes, 11.5% had paternal diabetes, and 1.7% had bilineal diabetes. Relative to individuals without parental diabetes, the age-adjusted ORs (95% CI) for offspring type 2 diabetes or abnormal glucose tolerance (fasting plasma glucose ≥6.1 mmol/l or 2-h postchallenge glucose tolerance ≥7.8 mmol/l) among individuals with maternal diabetes were 3.4 (2.3–4.9) and 2.7 (2.0–3.7), respectively; among individuals with paternal diabetes were 3.5 (2.3–5.2) and 1.7 (1.2–2.4), respectively; and among individuals with bilineal diabetes were 6.1 (2.9–13.0) and 5.2 (2.6–10.5), respectively. Although maternal and paternal diabetes conferred equivalent risk for offspring type 2 diabetes, offspring with maternal diabetes were slightly more likely to have abnormal glucose tolerance compared with those with paternal diabetes (OR 1.6, 95% CI 1.1–2.4). Offspring with maternal diabetes and an age of onset of <50 years had marked increased risk for both type 2 diabetes (9.7, 4.3–22.0) and abnormal glucose tolerance (9.0, 4.2–19.7). We conclude that risk ratios for offspring type 2 diabetes are consistent with a simple additive risk model, where risk when both parents are affected equals the sum of risk when either parent is affected. For maternal diabetes to confer excess risk for mild but not overt glucose intolerance, offspring of diabetic fathers may transit abnormal to impaired glucose tolerance relatively quickly, or diabetic mothers may transmit risk for a mild slowly progressive form of abnormal glucose tolerance in addition to overt diabetes. Very high risk for abnormal glucose homeostasis among offspring with young age–of–onset maternal diabetes is consistent with hypotheses that perinatal exposures increase diabetes risk. Given equivalent risk ratios for type 2 diabetes, fathers may transmit unique paternal genetic factors of similar strength to maternal environmental factors. *Diabetes* 49:2201–2207, 2000

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Type 2 diabetes is a heritable condition. Linkage analyses have led to identification of specific gene loci in a handful of families with diabetes (e.g., maturity diabetes onset of the young [MODY]) (1), but for the common form of type 2 diabetes, no specific gene for diabetes has been found (2,3). High concordance rates for type 2 diabetes in identical twins (4,5), increasing prevalence rates among populations with increasing admixture of Native-American gene sources (6,7), and aggregation of type 2 diabetes in families (8,9) all lend support to the existence of genetic determinants for type 2 diabetes. Family studies have estimated that risk for diagnosed type 2 diabetes increases approximately two- to fourfold when one or both parents are affected (10–14). In addition, some (13–20) but not all (10,21–23) studies suggest that offspring whose mothers had diabetes are more likely to develop diabetes themselves compared with offspring whose fathers had diabetes. A variety of hypotheses have been advanced to explain this apparent excess maternal transmission of diabetes, including unique maternal genetic and environmental effects (23). Study of parental transmission of diabetes is useful because the direction of causality is unequivocal, and the pattern of parental effects may give insight into the relative contributions of underlying maternal and paternal influences. Family data with glucose tolerance status of both parents and offspring assessed directly are available in high–diabetes risk

populations (10,18,21), but such data are sparse in lower-risk populations. We examined risk for type 2 diabetes and milder degrees of glucose intolerance, conditioned on directly ascertained parental diabetes status, among subjects of the population-based Framingham Offspring Study.

RESEARCH DESIGN AND METHODS

Participants.

Parents. The original cohort of the Framingham Heart Study consisted of 5,209 men and women, including 1,404 couples, randomly selected from the community of Framingham, Massachusetts, aged 30–62 years at the study onset in 1949 (24). At the time of recruitment, this community was essentially all Caucasian and of mixed European ethnic descent. Participants were examined biennially for the interval development of cardiovascular diseases and their risk factors, including diabetes. For this analysis, we assessed development of diabetes in the original cohort (the parents) through 1989 (the 20th examination cycle) after a mean duration of follow-up of 42 years, when the mean age of surviving parents was 79 ± 8 years (mean ± SD).

Parental diabetes in this study was defined as treatment with insulin or oral hypoglycemic medications, a casual plasma glucose level ≥11.1 mmol/l at any examination, or a plasma glucose level ≥11.1 mmol/l 1 h after a 50-g oral glucose tolerance test (OGTT) administered at examination cycle 10. We used more stringent blood glucose criteria than the previously published Framingham Study criteria for diagnosis of diabetes (25) to improve consistency with World Health Organization (WHO) criteria (26) and specificity of the parental diabetes phenotype. The Framingham cohort is a low–diabetes risk population: using more lenient random glucose criteria (≥8.3 mmol/l), we previously established that the incidence of diabetes among Framingham men aged 50–59 years was 5.7 cases per 1,000 persons per year—about one-tenth the rate among similar Pima men (27). We assumed that parental diabetes was type 2 diabetes, based on extremely low rates of type 1 diabetes in this population (see below) and on high rates of type 2 diabetes in U.S. national survey estimates of Caucasian populations (1). The age of onset of parental diabetes was defined as the parent's age at the examination at which diabetes was first diagnosed.

Offspring. Subjects of the Framingham Offspring Study are the natural children of the original Framingham Heart Study cohort families, aged 12–58 years old at the first offspring examination in 1971–1975 (28). Out of 1,404 original nuclear families, 2,629 children from 1,303 families completed 20 years of quadrennial follow-up through 1995, the fifth examination cycle (January 1991 through June 1995). Removing 100 with missing glucose tolerance status and 2 with type 1 diabetes left 2,527 subjects (1,201 men and 1,326 women) with both known glucose tolerance status and known parental diabetes status.

We measured plasma glucose with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA). Glucose assays were run in duplicate and the intra-assay coefficient of variation ranged from 2 to 3%, depending on the assayed glucose level. We defined offspring obesity as a baseline BMI (assessed at examination 1) exceeding 27.3 kg/m² in women or 27.8 kg/m² in men, corresponding to ~120% ideal body weight (29).

Offspring diabetes diagnoses. We ascertained offspring diabetes status using two methods. First, based on 20 years of observation, 103 offspring were classified with diagnosed diabetes if the fasting plasma glucose level was ≥7.8 mmol/l at any two examinations or they reported hypoglycemic drug therapy at any examination. Of these, 2 individuals younger than 35 years at diagnosis and requiring subsequent continuous insulin therapy were considered to have type 1 diabetes and excluded, leaving 101 with diagnosed type 2 diabetes. The age of onset of offspring-diagnosed diabetes was defined as the age at the first examination where these diagnostic criteria were met. We calculated the cumulative incidence of diagnosed diabetes using Kaplan-Meier product limit estimates, with diabetes age of onset as the time failure variable and nondiabetic subjects censored at their age at examination 5 (30).

Second, we used an OGTT at the fifth examination cycle to categorize the glucose tolerance status of subjects without diagnosed diabetes. After an overnight fast, plasma samples were drawn from all 2,527 study subjects for glucose measurement. A 75-g OGTT was administered according to WHO standards (26) to 2,426 subjects without diagnosed diabetes, and 2-h postchallenge glucose levels were measured. Subjects were classified with normal glucose tolerance (*n* = 1,943) if the fasting plasma glucose level was <6.1 mmol/l and the 2-h postchallenge plasma glucose level was <7.8 mmol/l, with abnormal glucose tolerance if either the fasting or postchallenge glucose levels were above normal (*n* = 584 including diabetes), and with OGTT-detected diabetes if either the fasting plasma glucose level was ≥7.8 mmol/l or the 2-h postchallenge glucose level was ≥11.1 mmol/l (*n* = 115) (26,31). Offspring with diagnosed and OGTT-detected diabetes were grouped together (and referred to as having type 2 diabetes; *n* = 216) for all analyses except age of onset analyses, where only those with diagnosed diabetes were considered.

Statistical analysis. We performed analyses for sexes combined and for men and women separately using the SAS statistical package (32). Statistical significance was defined as a two-tailed *P* value <0.05. We classified offspring as having no parent, mother only (maternal), father only (paternal), or both parents (bilineal) with diabetes. We also classified both parental and offspring diabetes as young age of onset (<50 years old) or older onset (≥50 years old). Because observations within families are not independent of one another, we used mixed effects analysis of variance models, which account for lack of independence among observations, to calculate and compare age, baseline BMI, plasma glucose levels, and diagnosed diabetes age of onset among offspring according to parental diabetes status (33). We adjusted *P* values in multiple pairwise comparisons using the Tukey method (34).

We used generalized estimating equations (35), which, like mixed effects models, account for lack of independence among observations, to calculate odds ratios (ORs) and 95% CIs for offspring glucose tolerance categories. Models included terms for offspring age (used as a continuously distributed variable), maternal diabetes only, paternal diabetes only, and bilineal diabetes, with offspring with no diabetic parents as the referent group, except in models assessing possible maternal excess transmission, in which offspring with paternal diabetes were used as the referent group. We also calculated the prevalence of parental diabetes among the 216 offspring with previously diagnosed and OGTT-diagnosed diabetes, using the χ^2 test to compare differences in the prevalence of maternal and paternal diabetes.

RESULTS

The 2,527 offspring came from 1,303 nuclear families with one (*n* = 567 families, 22.4% of families), two (*n* = 846, 33.5%), three (*n* = 588, 23.3%), four (*n* = 324, 12.8%), five (*n* = 90, 3.6%), six (*n* = 84, 3.3%), or seven (*n* = 28, 1.1%) siblings per family. In these families, the prevalence of a history of maternal diabetes was 23.6% (95% CI 21.3–25.9) and of paternal diabetes was 25.6% (23.2–27.9); among these mothers and fathers, the mean age of onset of diabetes was 60 ± 10 years.

Among the offspring, 1,929 (76.3%) had no parental diabetes, 265 (10.5%) had maternal diabetes, 291 (11.5%) had paternal diabetes, and 42 (1.7%) had bilineal diabetes. Distributions of parental diabetes were similar when comparing offspring men to women. The prevalence of diagnosed and OGTT-detected diabetes was higher in men than in women (10.0 vs. 7.2%; *P* = 0.01), as was the prevalence of abnormal glucose tolerance (men, 24.9%, vs. women, 21.5%; *P* = 0.04). Despite these differences, there was no interaction by offspring sex on associations between parental diabetes and levels of fasting or postchallenge plasma glucose levels or categorical diabetes or abnormal glucose tolerance (*P* > 0.08 for all interaction terms). Because parental effects were similar among both male and female offspring, we only present sex-combined results. The cumulative incidence of offspring-diagnosed diabetes at age 60 years was 5.1% (95% CI 3.8–6.3) and at age 70 years was 14.0% (10.4–17.5).

The cumulative distributions of fasting and postchallenge glucose levels, stratified by parental diabetes status, are shown in Fig. 1. The cumulative distributions of fasting glucose levels among offspring with parental diabetes were shifted toward higher glucose levels relative to individuals without parental diabetes, with the distribution of individuals with maternal diabetes shifted higher relative to individuals with paternal diabetes. Thus, at each threshold used as a criterion to classify glucose tolerance (vertical lines), a higher proportion of offspring with parental diabetes relative to those without parental diabetes exceeded that value. For example, 43% of offspring with bilineal diabetes had fasting glucose levels ≥6.1 mmol/l, whereas 29% with maternal diabetes, 16% with paternal diabetes, and 11% without parental diabetes had fasting plasma glucose levels exceeding this
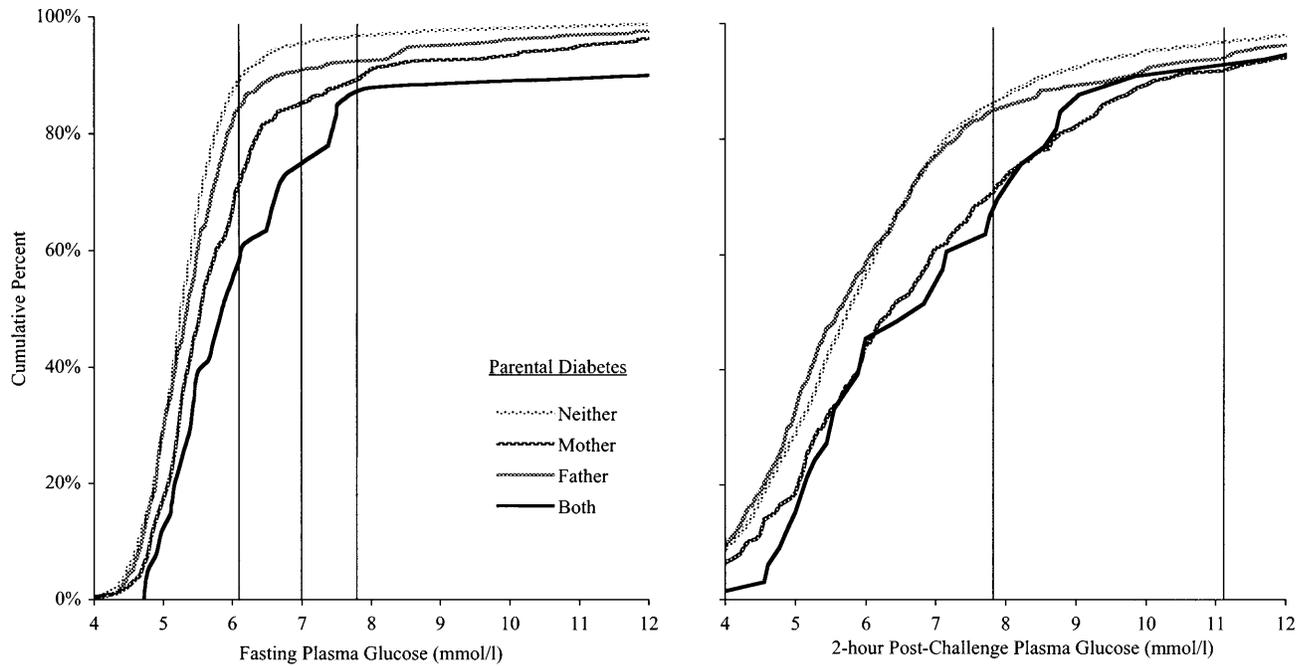
FIG. 1. Cumulative distributions of fasting ($n = 2,527$) and 2-h postchallenge ($n = 2,426$) plasma glucose levels among Framingham Offspring Study subjects, stratified by parental diabetes status. Thresholds used as criteria to classify glucose tolerance categories are indicated by vertical lines. A larger proportion of offspring with parental diabetes relative to offspring without parental diabetes exceed each threshold, and a larger proportion of offspring with maternal diabetes relative to offspring without paternal diabetes exceed each threshold.

threshold. For the cumulative distribution of postchallenge glucose levels, a higher proportion of offspring with maternal or bilineal diabetes relative to those with none or paternal diabetes exceeded the threshold defining impaired glucose tolerance: 35% with bilineal diabetes, 30% with maternal diabetes, 16% with paternal diabetes, and 14% without parental diabetes had fasting plasma glucose levels ≥7.8 mmol/l. The prevalence of subjects in each glucose tolerance category, stratified by age at examination 5, is shown in Table 1.

Although offspring with paternal diabetes were younger at examination 5 compared with those with maternal diabetes (51 vs. 56 years, $P = 0.0005$), adjustment for offspring age did not alter patterns of risk for abnormal glucose homeostasis associated with parental diabetes (Table 2). Offspring with maternal diabetes had a 2.5- to 3.5-fold increased age-adjusted risk, offspring with paternal diabetes a 1.4- to 3.5-fold increased risk, and offspring with bilineal parental diabetes were three to six times more likely than those without

TABLE 1
Age-stratified prevalence of plasma glucose diagnostic thresholds, abnormal glucose tolerance, and type 2 diabetes, by parental diabetes

	Parental diabetes			
	Neither	Mother	Father	Both
n				
<50 years old	709	77	123	13
≥50 years old	1,220	188	168	29
Fasting plasma glucose ≥6.1 mmol/l				
<50 years (%)	4	18	14	46
≥50 years (%)	15	33	17	41
2-h Postchallenge glucose ≥7.8 mmol/l				
<50 years (%)	6	17	10	27
≥50 years (%)	19	36	20	39
Abnormal glucose tolerance				
<50 years (%)	9	26	16	54
≥50 years (%)	26	48	32	55
Type 2 diabetes				
<50 years (%)	1	8	7	23
≥50 years (%)	9	24	19	28

Subjects with abnormal glucose tolerance had either fasting plasma glucose ≥6.1 mmol/l or 2-h postchallenge glucose ≥7.8 mmol/l and includes diabetes; type 2 diabetes includes both diagnosed and OGTT-detected diabetes.

TABLE 2
Age-adjusted ORs for plasma glucose diagnostic thresholds, abnormal glucose tolerance, and type 2 diabetes, by parental diabetes

	Parental diabetes		
	Mother	Father	Both
Fasting plasma glucose ≥6.1 mmol/l	3.0 (2.2–4.2)	1.8 (1.3–2.7)	6.2 (3.1–12.5)
2-h Postchallenge glucose ≥7.8 mmol/l	2.5 (1.8–3.4)	1.4 (0.95–2.0)	3.3 (1.5–7.3)
Abnormal glucose tolerance	2.7 (2.0–3.7)	1.7 (1.2–2.4)	5.2 (2.6–10.5)
Type 2 diabetes	3.4 (2.3–4.9)	3.5 (2.3–5.2)	6.1 (2.9–13.0)

Data are ORs (95% CI) adjusted for age as continuously distributed. Referent groups are offspring without parental diabetes. Subjects with abnormal glucose tolerance had either fasting plasma glucose ≥6.1 mmol/l or 2-h postchallenge glucose ≥7.8 mmol/l and includes diabetes; type 2 diabetes includes both diagnosed and OGTT-detected diabetes.

parental diabetes to meet abnormal glucose homeostasis criteria. In addition, further adjustment for baseline BMI did not substantially attenuate risk for offspring abnormal glucose homeostasis, even though offspring with parental diabetes were more obese at baseline than those without parental diabetes (BMI 26.2 ± 4.9 vs. 25.0 ± 4.1 kg/m^2, $P = 0.0001$) and greater offspring baseline BMI–increased risk for subsequent type 2 diabetes (age-adjusted OR, 95% CI, for a 1.0 kg/m^2 increase in BMI: 1.18, 1.15–1.21). The age- and BMI-adjusted OR (95% CI) for offspring type 2 diabetes among individuals with maternal diabetes was 2.8 (1.9–4.1), among those with paternal diabetes was 3.0 (2.0–4.5), and among those with bilineal diabetes was 6.0 (2.8–12.7). The age- and BMI-adjusted OR (95% CI) for abnormal glucose tolerance among individuals with maternal diabetes was 2.4 (1.8–3.3), among those with paternal diabetes was 1.5 (1.1–2.1), and among those with bilineal diabetes was 4.9 (2.4–9.9).

Maternal and paternal diabetes conferred equal risk for offspring type 2 diabetes, but offspring with maternal diabetes were at excess risk for exceeding subdiabetic glucose intolerance criteria (with paternal diabetes as the referent group, age-adjusted OR [95% CI] for maternal diabetes predicting offspring fasting plasma glucose ≥6.1 mmol/l: 1.6 [1.04–2.6]; ≥7.8 mmol/l: 1.8 [1.1–2.8]; abnormal glucose tolerance: 1.6 [1.1–2.4]; type 2 diabetes: 1.0 [0.6–1.6]). In addition, the prevalence of a history of maternal diabetes (23%) and paternal diabetes (18%) among the 216 offspring with type 2 diabetes was not statistically different ($P = 0.08$).

Maternal diabetes age of onset had a marked effect on risk for offspring abnormal glucose homeostasis (Table 3).

Offspring with maternal diabetes age of onset <50 years had a 7- to almost 10-fold increased odds of meeting criteria for abnormal or diabetic glucose tolerance compared with individuals without parental diabetes, whereas individuals with older maternal diabetes age of onset had only a 2- to 3-fold increased odds. Offspring with paternal diabetes of either young or old age of onset had only two- to fivefold increased odds of abnormal glucose homeostasis compared with offspring without parental diabetes. Maternal diabetes age of onset also appeared to influence the age of onset of offspring with diagnosed diabetes. Even after adjusting for the younger age at examination 5 of diagnosed diabetic offspring with young maternal diabetes age of onset (Table 4), these subjects were significantly younger at diagnosis (47 years, $P < 0.02$ for all pairwise comparisons) than those with older maternal or any paternal diabetes age of onset (all >54 years).

DISCUSSION
The Framingham Offspring Study provides an opportunity to examine parental transmission of glucose intolerance in a community-based population at relatively low risk for diabetes. Glucose tolerance phenotypes were assessed directly among both parents and offspring over several decades of follow-up and with an OGTT at the most recent offspring examination. We defined type 2 diabetes in both parents and offspring using the most stringent diagnostic criteria to maximize specificity of the phenotype but also defined an abnormal glucose tolerance category among offspring to examine transmission of mildly impaired glucose homeostasis.

TABLE 3
Age-adjusted ORs for plasma glucose diagnostic thresholds, abnormal glucose tolerance, and type 2 diabetes, by parental diabetes age of onset among offspring without bilineal diabetes

	Parental diabetes age of onset			
	Mother <50 years of age	Mother ≥50 years of age	Father <50 years of age	Father ≥50 years of age
n	34	231	39	252
Fasting plasma glucose ≥6.1 mmol/l	8.6 (4.1–18.4)	2.5 (1.7–3.6)	3.0 (1.3–7.0)	1.7 (1.1–2.6)
2-h Postchallenge glucose ≥7.8 mmol/l	7.4 (3.5–15.7)	2.0 (1.4–2.9)	0.6 (0.1–2.6)	1.5 (1.0–2.2)
Abnormal glucose tolerance	9.0 (4.2–19.7)	2.3 (1.6–3.1)	1.8 (0.8–4.0)	1.7 (1.2–2.4)
Type 2 diabetes	9.7 (4.3–22.0)	2.8 (1.8–4.2)	5.3 (2.1–13.6)	3.3 (2.1–5.2)

Data are ORs (95% CI), adjusted for age as continuously distributed. Referent groups are offspring without parental diabetes. Subjects with abnormal glucose tolerance had either fasting plasma glucose ≥6.1 mmol/l or 2-h postchallenge glucose ≥7.8 mmol/l and includes diabetes; type 2 diabetes includes both diagnosed and OGTT-detected diabetes.

TABLE 4
Age at examination 5 and age of diagnosed diabetes onset by parental diabetes age of onset among 94 Framingham Offspring Study subjects with diagnosed type 2 diabetes and without bilineal parental diabetes

| | | Parental diabetes age of onset | | | |
| | | Mother | | Father | |
	Neither	<50 years of age	≥50 years of age	<50 years of age	≥50 years of age
Subjects with type 2 diabetes (n)	49	3	22	5	15
Age at examination 5 (years)	64 ± 1.0	54 ± 4.2	68 ± 1.1	56 ± 3.3	57 ± 1.4
Age of diabetes onset (years)	59 ± 0.9	39 ± 4.8	61 ± 1.0	53 ± 3.7	49 ± 1.4
Age of diabetes onset, adjusted for age at examination 5 (years)	57 ± 0.7	47 ± 3.0*	57 ± 1.1	59 ± 2.3	54 ± 1.4

Data are means ± SE. *$P < 0.02$ for all pair-wise comparisons of offspring with young-onset maternal diabetes to those with no parental diabetes, older-onset maternal diabetes, or any paternal diabetes.

We found that risk for type 2 diabetes among offspring with a single diabetic parent was 3.5-fold higher and for those with two diabetic parents was 6-fold higher compared with offspring without parental diabetes. These risk ratios suggest a simple additive model for parental transmission of diabetes, in which risk when both parents are affected is a function of the sum of risk when either parent is affected: risk ratio$_{both}$ − 1 = (risk ratio$_{mother}$ − 1) + (risk ratio$_{father}$ − 1) (36). To the extent that type 2 diabetes is genetically transmitted, a simple additive model is consistent with transmission of two different noninteracting diabetogenic genes or closely allied sets of genes from each parent, or transmission of the same gene or sets of closely allied genes such that bilineal offspring receive a double dose of these loci. If some part of diabetes risk is environmentally transmitted, then maternal and paternal environmental exposures of equivalent strength may be acting, or maternal environmental exposures may be matched by equally strong paternal genetic exposures. The additive risk ratio model for offspring diabetes in the low–diabetes risk Framingham population is similar to that previously reported in high–diabetes risk Pima Indians, where the age-adjusted incidence rate ratio for offspring diabetes was 2.3 among Pimas with one diabetic parent and 4.5 among those with two diabetic parents compared with offspring with no diabetic parents (10). Similarity between the pattern of risk ratios in the Framingham and Pima populations suggests that whatever is actually heritable in diabetes transmission may be similar across human populations, regardless of overall absolute risk.

In the Framingham population, maternal and paternal diabetes conferred equal risk for overt type 2 diabetes among offspring in contrast to some (13–20), but not all (10,21–23), prior studies of parental diabetes transmission. However, offspring with maternal diabetes were more likely to have milder degrees of impaired glucose homeostasis compared with offspring with paternal diabetes, with 60–80% maternal excess relative odds for exceeding a fasting glucose threshold of 6.1 mmol/l, a 2-h postchallenge glucose level of 7.8 mmol/l, or both. There are a number of possible explanations why maternal diabetes might confer excess risk for mild, but not severe, glucose intolerance. First, offspring of diabetic mothers were a few years older at examination than offspring of diabetic fathers; some offspring with diabetic mothers might have had an age-related but not heritable form of glucose intolerance. However, statistical adjustment for differential age distribution

in offspring did not attenuate excess risk for mild glucose intolerance associated with maternal diabetes. Second, offspring with paternal diabetes may have moved more rapidly through the impaired prediabetic glucose tolerance state to overt diabetes than offspring with maternal diabetes, such that there were relatively few prevalent cases of abnormal glucose tolerance among offspring with paternal diabetes at examination 5. Alternatively, maternal diabetes may confer risk for a milder slowly progressive form of glucose intolerance (in addition to risk for frank type 2 diabetes), creating an excess of prevalent cases at the fifth examination.

It is possible that fetal exposures in diabetic mothers confer risk for mild slowly progressive glucose intolerance in some individuals and risk for progression to overt diabetic glucose intolerance in others. Prior evidence supports the concept that maternal diabetes is associated with an environmental transmission effect, over and above any putative genetic effect. The intrauterine environment in mothers with diabetes during pregnancy is associated with fetal undernutrition, low birth weight, insulin resistance, and adult type 2 diabetes (18,37–39). We found that maternal diabetes conferred excess risk for both impaired fasting glucose (fasting plasma glucose ≥6.1 mmol/l) and impaired glucose tolerance (postchallenge glucose ≥7.8 mmol/l), placing specific offspring at varying stages in the progression from normal to diabetic glucose tolerance (40). Longer follow-up will be required to determine whether there is a unique subset of subjects with mild glucose intolerance who do not progress to diabetes. We do not have data on diabetes before and during pregnancy but were able to classify some mothers with diabetes onset at <50 years of age— roughly, the childbearing years— and found that offspring of these mothers were at markedly increased risk for abnormal or diabetic glucose tolerance and for a younger age of onset of diagnosed diabetes, consistent with the global hypothesis that perinatal hyperglycemia confers a diabetogenic effect in offspring.

If in utero exposure is an important maternal mechanism increasing risk for overtly diabetic hyperglycemia, then based on comparable effect sizes among maternal and paternal diabetes, a unique paternal factor of similar strength to potential in utero factors may be in effect. Recent data in high–diabetes risk populations provide evidence for unique paternal genetic effects. Using family-based association methods in parent-offspring trios with type 2 diabetes, Huxtable et al. (41) reported exclusively paternal transmission

of class III alleles at the variable number tandem repeat regulatory polymorphism of the insulin gene (*INS*-VNTR). The *INS*-VNTR alleles lie <5 kb upstream from the *IGF2* locus, a known mediator of fetal growth and development (42). Maternal imprinting on allelic variants at the *INS-IFG2* locus has been proposed to constitute a genetic link between maternal intrauterine exposures, paternal alleles, and type 2 diabetes (41). Data from Pima Indians also suggest the existence of a unique paternal factor associated with low birth weight. In Pimas, fathers of low–birth weight infants were at increased risk for diabetes, and low–birth weight infants were at increased risk for diabetes only when the father, but not the mother, had diabetes (43). Lack of birth weight data prevented our examination of interactions among parental diabetes, offspring infant birth weight, and adult diabetes. Nonetheless, our data are consistent with overall maternal and paternal effects of equal strength, interacting to produce an additive increased risk for offspring diabetes when both parents are affected.

In conclusion, Framingham Offspring Study data suggest a simple additive risk model for transmission of type 2 diabetes, with equivalent maternal and paternal effects on risk for overt offspring diabetes but a small excess maternal risk for milder nondiabetic offspring glucose tolerance. For this model to occur, offspring of diabetic fathers may move through abnormal to diabetic glucose tolerance relatively quickly compared with offspring of diabetic mothers, or diabetic mothers may transmit a mild slowly progressive form of abnormal glucose tolerance in addition to risk for overt diabetes. Offspring whose mothers developed diabetes at a relatively young age had a marked excess of both impaired and diabetic glucose tolerance, consistent with the hypothesis that perinatal exposures increase diabetes risk. Given equivalent risk ratios for type 2 diabetes, fathers may transmit unique paternal genetic factors of similar strength to maternal environmental factors.

ACKNOWLEDGMENTS

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