Maternal Family History of Diabetes Is Associated With a Reduced Risk of Cardiovascular Disease in Women With Type 2 Diabetes

The Fremantle Diabetes Study

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OBJECTIVE — To investigate whether parental family history of diabetes influences cardiovascular outcomes in type 2 diabetes.

RESEARCH DESIGN AND METHODS — We studied 1,294 type 2 diabetic patients (mean age 64.1 years, 51.2% female) recruited to a community-based cohort study from 1993 to 1996 and followed until mid-2006. A data linkage system assessed all-cause and cardiac mortality, incident myocardial infarction, and stroke. Cox proportional hazards modeling was used to determine the influence of maternal or paternal family history on these outcomes.

RESULTS — A maternal family history of diabetes was reported by 20.4% of the cohort, 8.3% reported paternal family history, and 2.0% reported both parents affected. Maternal and paternal family history was associated with earlier age of diabetes onset, and maternal family history was associated with worse glycemic control. For all patients, maternal family history was significantly associated with reduced risk of all-cause mortality and cardiac mortality. When analyzed by sex, maternal family history had no effect on male patients, whereas female patients with diabetic mothers had significantly reduced hazard ratios for death from all causes (0.63 [95% CI 0.41–0.96]; $P = 0.033$), for death from cardiac causes (0.32 [0.14–0.72]; $P = 0.006$), and for first myocardial infarction (0.45 [0.26–0.76]; $P = 0.003$). Paternal family history status was not associated with these outcomes.

CONCLUSIONS — A maternal family history of diabetes confers relative protection against cardiovascular disease in female patients but not in male patients with type 2 diabetes. Paternal family history is associated with risks equivalent to those without a family history of diabetes. Some of the clinical heterogeneity of type 2 diabetes is related to maternal transmission effects with differential impact on male and female patients.

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The complex etiology of type 2 diabetes involves both genetic components and environmental exposures. In type 2 diabetes, there is a well documented association between a family history of the disease and its development (1,2). Maternal and paternal family histories of diabetes are both associated with an earlier age of onset (2–4), and this effect is more marked when multiple family members are affected (5). In addition, intrauterine exposure to diabetes increases the risk of diabetes in offspring (6), which may help explain the reported excess maternal transmission (7,8).

Patients with familial diabetes have relatively poor glycemic control, but few other clinical differences have been reported (4,5,9,10). An early age of onset and poor glycemic control would both be expected to have a negative impact on the development of chronic complications, but no such longitudinal data have been published. In the present study, we examined relationships among parental diabetes and important clinical outcomes in type 2 diabetes, including incident coronary heart disease (CHD) and all-cause and cardiac mortality in a large community-based sample of patients with type 2 diabetes. We hypothesized that familial diabetes would indicate worse clinical outcomes. We investigated potential relationships in male and female patients separately, given the known differences in CHD incidence between men and women with diabetes (11).

RESEARCH DESIGN AND METHODS

— The present sample comprised all participants with type 2 diabetes enrolled in the Fremantle Diabetes Study (FDS), a longitudinal observational study conducted from a postcode-defined urban Australian community of 120,097 people. Descriptions of recruitment, sample characteristics including classification of diabetes type, and details of nonrecruited patients have been published previously (12,13). Of 2,258 diabetic patients identified between 1993 and 1996, 1,426 (63%) were recruited and 1,294 had type 2 diabetes. The study protocol was approved by the Fremantle Hospital Human Rights Committee, and all subjects gave informed consent before participation.

Clinical assessment

Each participant underwent a comprehensive assessment at FDS entry that

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comprised *1*) a standard questionnaire including questions on diabetes symptoms at onset, self–glucose monitoring, attendance at diabetes education/dietitian sessions, lifestyle factors, education, self-assessed ethnicity, fluency with English, and knowledge of diabetes (12); *2*) a detailed physical examination; and *3*) the provision of fasting blood and urine samples for automated biochemical tests performed in a single laboratory. As part of *1*) above, all participants were asked to provide details of relatives with known diabetes (including a specific enquiry as to the status of mother, father, grandparents, son, daughter, grandchildren, brother, sister, uncle, aunt, and other) and their respective diabetes treatment status (whether insulin or tablet/diet treated).

Complications were identified using standard definitions (13). Peripheral neuropathy was defined as a score >2 of 8 on the Michigan Neuropathy Screening Instrument clinical portion. Retinopathy was taken as any grade detected by direct/indirect ophthalmoscopy and/or ophthalmologist assessment. Nephropathy was defined as a first-morning urinary albumin-to-creatinine ratio ≥3.0 mg/mmol. Self-reported stroke/transient ischemic attack were amalgamated with prior hospitalizations to define baseline cerebrovascular disease status. Patients were classified as having CHD if there was a self-reported history of or hospitalization for myocardial infarction, angina, revascularization, or angioplasty. Peripheral arterial disease was considered to be present when the ankle-to-brachial index was ≤0.90 or by the presence of a diabetes-related amputation.

Incident cardiovascular disease and mortality

The Hospital Morbidity Data System records all public and private hospital separations in Western Australia and, together with the death register, forms part of the Western Australia Data Linkage System (WADLS) (14). The FDS database was linked with the WADLS to provide morbidity/mortality data from 1 January 1993 until the end of June 2006. Hospitalizations for CHD and cerebrovascular disease were extracted from WADLS to calculate prevalent and incident myocardial infarctions and strokes. The causes of death were reviewed independently by two of the authors (D.G.B. and T.M.E.D.) and classified as being due to cardiac causes or not under the system used in the UK Prospective Diabetes Study (15). When there was disagreement between raters, a final consensus decision was reached.

Statistical methods

Pancreatic β-cell function and insulin sensitivity were estimated from fasting serum glucose (FSG) and serum insulin concentrations using homeostasis model assessment (16). All data were analyzed using SPSS for Windows (version 14.0.2). Because GHb, FSG, serum triglycerides, urinary albumin-to-creatinine ratio, insulin sensitivity, and pancreatic β-cell function were not normally distributed, they were log-transformed before analysis. Data are reported as means ± SD, geometric mean (SD range), medians (interquartile range), or percentages. ANOVA and Fisher's exact tests were used to test equality of means for normally distributed continuous and categorical variables, respectively. Variables with a nonparametric distribution were analyzed using the Kruskal-Wallis test. If differences were detected, pairwise comparison with a Student *t* test, Fisher exact test, or Mann-Whitney test was undertaken. Multivariate linear regression analysis was used to investigate effects on glycemic and blood pressure control after appropriate adjustment. Cox proportional hazards modeling (with forward conditional, variable entry, and removal at $P < 0.05$ and > 0.10, respectively) was used to determine independent predictors of all-cause mortality, cardiac mortality, first-time incident myocardial infarction, and first incident stroke (subjects with prior events were excluded from relevant models). All clinically plausible variables were considered for entry into the models before family history status was entered.

RESULTS

Baseline sample characteristics

The patient sample was aged 64.1 ± 11.3 years and 51.2% were women. A parental family history of diabetes was reported by 397 patients (30.7%), of whom 264 (20.4%) had a maternal family history, 107 (8.3%) had a paternal family history, and 26 (2.0%) had both parents affected (Table 1). Diabetes onset occurred at a significantly younger age in patients with parental diabetes. At the time of baseline assessment, they were also younger but had duration of diabetes similar to that of patients without a family history. Patients with a maternal family history had significantly higher FSG and GHb levels. Systolic blood pressure was lower with both maternal and paternal family histories.

After adjustment for age, diabetes duration, and treatment type, both FSG and GHb remained significantly higher with maternal family history [β ln(FSG) 0.05 (95% CI 0.01–0.09) mmol/l; $P = 0.017$ and ln(GHb) 0.05% (0.02–0.07); $P = 0.001$], but not with a paternal family history ($P \geq 0.39$). After adjustment for age, no significant difference in systolic blood pressure levels was seen with maternal or paternal family histories. There were no differences by family history in proportions with GAD antibody positivity, pancreatic β-cell function, or insulin sensitivity, exercise levels, alcohol intake, or proportions taking blood pressure–lowering or lipid-lowering medications (data not shown).

Family history, mortality, myocardial infarction, and stroke

By the end of June 2006, crude all-cause mortality rates were significantly lower in patients with maternal and paternal family histories (Table 1). In Cox regression models (Table 2), we examined the effect of family history unadjusted (model 1), after adjustment for age and sex (where appropriate, model 2), and after adjustment for identified relevant variables (model 3, variables listed in supplementary Table 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-0147/DC1). In adjusted models, maternal or paternal family history was entered into the most parsimonious model to assess whether either was an independent determinant of outcome. For all patients, maternal family history was associated with a significantly reduced risk of death from all causes and from cardiac causes, whereas there was a trend toward a reduction in the risk of incident myocardial infarction (Table 2). When analyzed by sex, the protective effect of maternal family history on all-cause and cardiac mortality was only significant in female patients and was significant for incident myocardial infarction in women. Paternal family history was not associated with differences in clinical outcomes.

Maternal family history, diabetes presentation, and health-related behaviors

To explore possible reasons for a protective effect of a maternal family history, we assessed relationships with diabetes pre-

Table 1—*Demographic and baseline clinical characteristics and subsequent crude mortality rates of the sample by parental family history*

	Family history				
	No	Maternal	Paternal	Both	*P*
n	897	264	107	26	
Age (years)	65.5 ± 10.8	61.4 ± 11.7†	60.0 ± 11.5†	58.0 ± 11.8†	<0.001
Age at diagnosis (years)	59.4 ± 11.1	55.6 ± 11.8†	53.1 ± 12.5†	51.8 ± 13.8†	<0.001
Diabetes duration (years)	4.0 [1.0–9.0]	4.0 [0.9–9.0]	4.0 [0.9–10.0]	4.0 [0.3–8.5]	0.99
Male sex (%)	50.2	42.8	53.3	42.3	0.12
Ethnic background (%)					
Anglo-Celt	65.6	56.1	63.6	57.7	
Southern European	16.7	22.7	20.6	23.1	
Other European	8.7	9.5	6.5	0.0	NV
Asian	2.7	2.7	5.6	19.2	
Mixed/other	5.2	6.4	2.8	0.0	
Indigenous	1.1	2.7	0.9	0.0	
BMI (kg/m^2)	29.3 ± 5.4	30.4 ± 5.5†	30.0 ± 5.3	29.6 ± 5.4	0.019
Waist (% overweight/obese)	84.2	92.7†	87.6	80.8	0.002
Systolic blood pressure (mmHg)	152 ± 24	148 ± 22†	147 ± 21†	146 ± 23	0.009
Diastolic blood pressure (mmHg)	81 ± 12	80 ± 10	80 ± 10	77 ± 8	0.38
Fasting glucose (mmol/l)	8.2 [6.8–10.6]	8.9 [7.2–11.7]†	8.4 [6.6–10.5]	8.9 [6.9–10.9]	0.013
GHb (%)	7.3 [6.3–8.7]	7.9[6.7–9.2]†	7.2 [6.4–8.7]	8.0 [6.6–8.9]	0.001
Diabetes treatment (%)					
Diet alone	32.0	27.3	42.1	38.5	
Oral agents	55.3	61.0	49.5	57.7	0.10
Insulin (± oral agents)	12.7	11.7	8.4	3.8	
Total cholesterol (mmol/l)	5.5 ± 1.2	5.5 ± 1.0	5.5 ± 1.0	5.5 ± 1.2	0.97
HDL cholesterol (mmol/l)	1.06 ± 0.33	1.05 ± 0.30	1.08 ± 0.35	1.10 ± 0.33	0.80
Serum triglyceride (mmol/l)	1.9 (1.1–3.4)	1.9 (1.1–3.2)	2.0 (1.2–3.3)	1.7 (1.0–2.9)	0.72
Cerebrovascular disease (%)	11.6	7.2	6.5	3.8	0.08
CHD (%)	29.1	25.8	19.6	26.9	0.18
Peripheral arterial disease (%)	30.0	30.3	24.5	15.4	0.28
Retinopathy (%)	16.0	18.4	17.8	4.0	0.17
Neuropathy (%)	33.7	26.3*	23.3*	12.0*	0.005
Albumin-to-creatinine ratio (mg/mmol)	3.2 (0.7–13.7)	3.2 (0.8–13.1)	3.0 (0.5–16.7)	1.7 (0.6–4.7)	0.19
Smoking status (%)					
Never smoked	45.1	46.9	33.3	52.0	
Former smoker	39.9	37.0	51.4	40.0	0.20
Current smoker	15.0	16.0	15.2	8.0	
All-cause mortality (%)	41.9	29.5†	34.0	11.5†	<0.001
Cardiac mortality (%)	17.9	8.7†	10.4	7.7	0.001

Data are means ± SD, geometric means (SD range), medians [interquartile range], or %. *$P < 0.05$; †$P < 0.01$ compared with no family history. NV, not valid.

sentation, self-care behaviors, and knowledge of diabetes. No statistical differences were found in mode of presentation at diagnosis (symptomatic or incidental), the nature of the presenting symptoms (thirst, polyuria, fatigue, weight loss, or visual blurring), the frequency of medical visits (family doctors, diabetes clinics, diabetes specialists, diabetes educators, and other medical specialists), or in the performance of self-monitoring of blood glucose. Female patients with either parent having diabetes had higher diabetes knowledge scores than patients without a family history ($P \leq 0.033$), but this was not seen in men with a parental family history.

CONCLUSIONS — The results of our longitudinal observational study are consistent with those of previous reports in showing that patients with a parental family history of diabetes develop diabetes ~5 years before their counterparts without a family history (2–5). We also found that our patients with a maternal family history had worse glycemic control. Despite these unfavorable features, female patients with a maternal family history had a lower risk of myocardial infarction and reduced all-cause and cardiac mortality. Because women with type 2 diabetes have a substantially increased risk of cardiovascular disease compared with nondiabetic women (11), these data suggest that diabetic women with a maternal family history have a risk of myocardial infarction and death that is intermediate between diabetic women without a family history and nondiabetic women. Male patients with a maternal family history and patients of either sex with a paternal family history had outcomes comparable to those in patients without a family history.

In explaining these findings, consideration needs to be given to the relative impact of maternal versus paternal family history on cardiovascular disease in diabetes and why a benefit should be confined to females. Familial disease can be transmitted by genetic and nongenetic in-

Table 2—*Hazard ratios for clinical outcomes in patients with type 2 diabetes by parental history*

	No family history			Family history				
	No. patients	No. events	Absolute risk*	No. patients	No. events	Absolute risk*	Log-rank *P* value	Hazard ratios (95% CI)
All patients: maternal history								
All-cause mortality								
Model 1†	1,001	410	43.1	290	81	26.4	<0.001	0.60 (0.48–0.77)
Model 2‡								0.81 (0.64–1.03)
Model 3§								0.69 (0.52–0.92)
Cardiac mortality								
Model 1†	1,001	172	18.1	290	25	8.2	<0.001	0.45 (0.30–0.69)
Model 2‡								0.61 (0.40–0.93)
Model 3§								0.50 (0.31–0.82)
Myocardial infarction								
Model 1†	977	227	25.6	281	51	17.9	0.023	0.70 (0.52–0.95)
Model 2‡								0.91 (0.67–1.24)
Model 3§								0.73 (0.52–1.03)
Stroke								
Model 1†	998	106	11.5	290	26	8.6	0.19	0.75 (0.49–1.15)
Model 2‡								1.00 (0.65–1.54)
Model 3§								0.73 (0.45–1.20)
All patients: paternal history								
All-cause mortality								
Model 1†	1,159	452	40.3	132	39	28.8	0.039	0.71 (0.51–0.98)
Model 2‡								0.92 (0.66–1.28)
Model 3§								1.06 (0.73–1.54)
Cardiac mortality								
Model 1†	1,159	184	16.4	132	13	9.6	0.06	0.59 (0.33–1.03)
Model 2‡								0.76 (0.43–1.34)
Model 3§								0.96 (0.52–1.78)
Myocardial infarction								
Model 1†	1,128	258	24.7	130	20	15.6	0.049	0.64 (0.40–1.00)
Model 2‡								0.79 (0.50–1.25)
Model 3§								0.98 (0.60–1.61)
Stroke								
Model 1†	1,156	120	11.0	132	12	9.0	0.50	0.81 (0.45–1.47)
Model 2‡								1.10 (0.61–2.00)
Model 3§								1.15 (0.60–2.21)
Women: maternal history								
All-cause mortality								
Model 1†	495	179	36.9	166	41	22.8	0.004	0.61 (0.44–0.86)
Model 2‡								0.81 (0.58–1.14)
Model 3§								0.63 (0.41–0.96)
Cardiac mortality								
Model 1†	495	77	15.9	166	10	5.6	0.001	0.35 (0.18–0.68)
Model 2‡								0.47 (0.24–0.91)
Model 3§								0.32 (0.14–0.72)
Myocardial infarction								
Model 1†	485	104	22.6	161	23	13.7	0.029	0.61 (0.39–0.96)
Model 2‡								0.83 (0.53–1.31)
Model 3§								0.45 (0.26–0.76)
Stroke								
Model 1†	495	52	11.0	166	14	7.9	0.27	0.72 (0.40–1.30)
Model 2‡								0.93 (0.51–1.67)
Model 3§								0.73 (0.40–1.36)

(continued)

heritance factors. The latter include epigenetic mechanisms such as functional imprinting and nonepigenetic mechanisms such as familial behavioral and cultural effects. With maternal transmission of diabetes, additional mechanisms include intrauterine effects on fetal growth and development that lead to persistent changes in later life and transfer of mater-

Table 2—*Continued*

	No family history			Family history				
	No. patients	No. events	Absolute risk*	No. patients	No. events	Absolute risk*	Log-rank *P* value	Hazard ratios (95% CI)
Women: paternal history								
All-cause mortality								
Model 1†	597	206	34.5	64	14	20.4	0.047	0.58 (0.34–1.00)
Model 2‡								0.82 (0.48–1.42)
Model 3§								1.20 (0.64–2.25)
Cardiac mortality								
Model 1†	597	83	13.9	64	4	5.8	0.08	0.42 (0.15–1.14)
Model 2‡								0.60 (0.22–1.65)
Model 3§								0.79 (0.25–2.56)
Myocardial infarction								
Model 1†	583	121	21.6	63	6	9.0	0.032	0.42 (0.19–0.95)
Model 2‡								0.59 (0.26–1.34)
Model 3§								0.62 (0.25–1.52)
Stroke								
Model 1†	597	64	11.0	64	2	2.9	0.045	0.26 (0.06–1.07)
Model 2‡								0.37 (0.09–1.50)
Model 3§								0.40 (0.10–1.63)
Men: maternal history								
All-cause mortality								
Model 1†	506	231	49.6	124	40	31.5	0.006	0.63 (0.45–0.88)
Model 2‡								0.80 (0.57–1.12)
Model 3§								0.78 (0.53–1.14)
Cardiac mortality								
Model 1†	506	95	20.4	124	15	11.8	0.044	0.58 (0.33–0.99)
Model 2‡								0.74 (0.43–1.29)
Model 3§								0.70 (0.39–1.27)
Myocardial infarction								
Model 1†	492	123	28.8	120	28	23.9	0.40	0.84 (0.56–1.26)
Model 2‡								0.99 (0.65–1.50)
Model 3§								0.92 (0.60–1.42)
Stroke								
Model 1†	503	54	12.0	124	12	9.6	0.48	0.80 (0.43–1.49)
Model 2‡								1.07 (0.57–2.01)
Model 3§								0.90 (0.47–1.75)
Men: paternal history								
All-cause mortality								
Model 1†	562	246	46.7	68	25	37.5	0.30	0.80 (0.53–1.21)
Model 2‡								0.96 (0.63–1.46)
Model 3§								1.03 (0.64–1.66)
Cardiac mortality								
Model 1†	562	101	19.2	68	9	13.5	0.31	0.71 (0.36–1.39)
Model 2‡								0.84 (0.42–1.68)
Model 3§								0.87 (0.41–1.81)
Myocardial infarction								
Model 1†	545	137	28.4	67	14	22.9	0.45	0.81 (0.47–1.40)
Model 2‡								0.91 (0.52–1.59)
Model 3§								0.98 (0.55–1.75)
Stroke								
Model 1†	559	56	11.0	68	10	15.4	0.33	1.40 (0.71–2.74)
Model 2‡								1.75 (0.88–3.45)
Model 3§								1.61 (0.79–3.26)

*Events per 1,000 person-years. †Model 1 is unadjusted. ‡Model 2 includes age and sex (where applicable). §Model 3 includes all variables in the respective most parsimonious models (supplementary Table 1).

nally inherited mitochondrial genes (6,8). The present study included the assessment of a range of biological, lifestyle, and behavioral factors, but we found no candidate explanatory variables among them. Lower baseline systolic blood pressure levels were seen with maternal and paternal family histories, but this effect did not persist after age adjustment. A study in Taiwanese patients found that a parental family history of diabetes conferred a lower risk of hypertension in type 2 diabetes (17), suggesting that further study of blood pressure control in relation to family history would be worthwhile. The women with diabetic parents in the present study had better knowledge of diabetes, but the women with a paternal family history also had greater knowledge without evident benefit, although there is evidence that knowledge alone does not influence cardiovascular outcomes in diabetes (18). Despite these negative findings, we cannot rule out the possibility that behavior related to family history may explain the results. For instance, subjects with a family history may be more likely to recognize the risk factors and symptoms of diabetes and thus receive a diagnosis and start appropriate management (including that for nonglycemic cardiovascular risk factors) at a relatively early stage.

We were not able to collect valid data on the age of onset of diabetes in the mothers, but the great majority are likely to have had type 2 diabetes. Human and animal studies have demonstrated that fetal exposure to maternal diabetes leads to a higher prevalence of impaired glucose tolerance in the offspring largely related to insulin secretory defects (6,8). More than 70% of women with gestational diabetes mellitus develop type 2 diabetes when followed for >10 years, and many women who develop diabetes but had not received a diagnosis of gestational diabetes mellitus are likely to have had some degree of glucose intolerance when pregnant (19,20). Therefore, in the present study, there may have been prenatal changes induced by maternal glucose intolerance in a proportion of patients with maternal family history. Because this mode of transmission of diabetogenic traits is also associated with adverse cardiovascular risk factors in offspring during early life (8,10,21), the present data indicate that there are qualitative differences in the cardiovascular risk that result from prenatal maternal factors compared with that seen in nonfamilial type 2 diabetes. One possible explanation is that fetal diabetogenic factors persist, whereas fetal nonglycemic cardiovascular risk factors wane with age.

There are several potential explanations as to why maternal family history had a differential effect in male and female patients. There are increasing reports of sex differences resulting from genetic and epigenetic transmission in a range of common complex disorders, including cardiovascular disease and type 2 diabetes (8,22). For example, sex differences were reported in an animal model of fetal imprinting in which male offspring developed hypertension, but females were protected (23). It is also possible that men give less accurate family histories, although studies on the analytical validity of family history reports do not indicate a sex bias (24).

The study strengths include the large and representative nature of the sample, the detailed nature of clinical and demographic assessment, and the completeness of ascertainment of the major clinical end points using a well-validated data linkage system. The major limitation relates to the method used to assess family history. Patients classified as having no family history of diabetes included those with limited or no knowledge of the health status of their relatives. This may have led to instances of a false-negative family history and thus an overestimation of the maternal transmission of diabetes because an unknown paternal status is more common in this situation (25). Other potential limitations include recall bias for family history, demonstrated to be minimal in diabetes (24), and a lack of statistical power to detect effects from paternal family history as the number of affected patients was relatively small. We were unable to distinguish gestational diabetes mellitus or the time of onset in the parents with diabetes and the study did not take account of other relevant family history such as having affected siblings.

In summary, the present study demonstrates that women with type 2 diabetes and a maternal family history of diabetes have a lower risk of myocardial infarction and death from cardiac causes than women without a family history of diabetes. These data indicate another source of heterogeneity in the clinical impact of type 2 diabetes and have relevance for understanding the pathophysiology, epidemiology, and public health impact of cardiovascular disease in women with type 2 diabetes.

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