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Can inaccuracy of reported parental history of diabetes explain the maternal transmission hypothesis for diabetes?

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Background	The mode of inheritance of type 2 diabetes mellitus is still under discussion. Several studies have suggested an excess maternal transmission, however, more recent studies could not always confirm these findings.
Methods	We investigated the frequency of a maternal and paternal history of diabetes among diabetic and non-diabetic subjects and assessed the association between diabetes and a parental history of diabetes among participants of the MONICA Augsburg study. As an extension to previous studies, unknown parental status was taken into account.
Results	Of the 542 diabetic probands, 25.3% reported a positive maternal history of diabetes and 10.9% reported a positive paternal history of diabetes. Among the 12 209 non-diabetic participants a positive maternal history was also more common than a positive paternal history (12.5% versus 7.1%). Conversely, an unknown paternal status was more common than an unknown maternal status in both groups (diabetic subjects: 27.9% versus 16.8%, non-diabetic subjects: 16.8% versus 8.4%). Adjusted odds ratios (OR) for the association between a parental history of diabetes and diabetes status were similar for a positive maternal (OR = 2.9, 95% CI : 2.3–3.6) and paternal history (OR = 2.8, 95% CI : 2.1–3.8) and for an unknown maternal (OR = 1.3, 95% CI : 1.0–1.8) and paternal history (OR = 1.5, 95% CI : 1.2–1.9).
Conclusion	Our findings do not support a strong excess maternal transmission of diabetes. Epidemiological biases and failure to account for 'don't know' responses may in part explain the previously observed predominance of a maternal history of diabetes.

Keywords	Diabetes, maternal transmission, parental history of diabetes, epidemiological biases
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A number of studies have reported a higher frequency of maternal compared to paternal history of diabetes among patients with type 2 (non insulin dependent) diabetes.[1–5] This observation led to the hypothesis that type 2 diabetes is predominantly transmitted maternally. One mechanism that has been proposed is that maternally inherited mitochondrial DNA mutations and deletions are important in the transmission of diabetes.[6–8] Other explanations include genetic imprinting[9] and environmental mechanisms such as the intrauterine environment[10] and behavioural risk factors passed on preferentially by the mother.[11–13] While all these mechanisms may be important in the transmission of diabetes they probably cannot explain the marked excess in maternal transmission suggested by the above-mentioned studies.

Of note, some studies did not observe excess maternal transmission of diabetes.[14–18] Ethnic differences in the transmission

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of diabetes have been suggested as one reason for the differing results but the observed differences could also be related to the almost inevitable epidemiological biases such as reporting bias and censoring bias that result from reliance on reported parental histories.[19] All studies observing excess maternal transmission of diabetes used proband's report as the basis to characterize parental history of diabetes. In most cases probands were not given the option to answer 'I don't know'. Therefore, it is difficult to quantify the effect of potential biases on the reported excess of maternal transmission of diabetes. To explore the impact of these biases we investigated the frequency of an unknown maternal and paternal status of diabetes in a population-based study and assessed the association between diabetes in the proband and a parental history of diabetes taking unknown parental status into account.

Subjects and Methods

Study population

From 1984 to 1995 three independent cross-sectional surveys have been conducted in the city of Augsburg (Germany) and the surrounding counties (Landkreise) within the framework of the multinational WHO MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) project. Details concerning the study design and methods have been described elsewhere.[20,21] Briefly, a total of 13 428 subjects (6703 women, 6725 men) participated in one or more of the three surveys. The response rates ranged from 79.3% in 1984/85 to 74.9% in 1994/95. Only data from the earliest survey was used if people had participated in two (n = 366) or three (n = 12) surveys. Subjects with missing values (as opposed to 'don't know') for parental history of diabetes or missing diabetes status (n = 8) and those who were unsure whether they had diabetes (total n = 669) were excluded leaving a total of 6421 women and 6330 men for the analysis presented in this paper. Among these, 240 women and 302 men reported having diabetes mellitus. We cannot determine the type of diabetes with certainty, but the number of subjects with type 1 diabetes was probably small since few cases were diagnosed before 40 years of age and treated only with insulin (n = 10 women, n = 14 men). Thus it can be assumed that the great majority of subjects had type 2 diabetes and therefore, the term type 2 diabetes will be used throughout this paper.

Definition of parental history of diabetes

In a personal interview subjects with living parents were asked: 'Does your mother (father) have diabetes?' Those with deceased parents were asked: 'Did your mother (father) have diabetes?' Probands could answer 'yes', 'no' or 'I don't know'. Subjects who did not know whether their mother (n = 31) or father (n = 148) were still living were assigned an unknown parental status of diabetes.

Statistical methods

Differences in the frequencies of parental history of diabetes between groups (e.g. men and women) were analysed with χ^2 tests. In the case of matched series (maternal and paternal history of a person) differences were tested by Mc Nemar's test. The association between the outcome personal diabetes and the exposure variables for parental history of diabetes were analysed using logistic regression analysis. The exposure variables maternal/paternal history of diabetes were categorized into three groups: negative, unknown, positive. In addition to the exposure variables, age (continuous), gender and survey were included in the models. To determine whether the associations between personal diabetes and a parental history of diabetes differed between men and women, models which included interaction terms between the parental history variables and gender were also considered. Furthermore, an interaction term between the parental history variables was entered into the models to evaluate whether the effect of a positive or unknown maternal or paternal status differed depending on the status for the other parental history variable. Odds ratios (OR) and the corresponding 95% CI were reported. All analyses were performed using the statistical software package SAS (Version 6.12, SAS Institute Inc., Cary, North Carolina). *P*-values <0.05 were stated as statistically significant.

Results

Frequency of an unknown parental status of diabetes (Table 1)

Parental history of diabetes was unknown for at least one parent in 21.2% of the subjects. Unknown paternal status was significantly more common than unknown maternal status (17.3% versus 8.8%, $P = 0.001$). This pattern was seen in females and males, in those <55 years and $\geqslant 55$ years and among diabetic and non-diabetic subjects.

Males were less likely to know the diabetes status of their parents than females. An even larger difference was seen between older and younger people. Unknown maternal as well as paternal status was more common among diabetic than among non-diabetic subjects (maternal history: $P = 0.001$; paternal history: $P = 0.001$). However, this difference was partly explained by age since people with diabetes were on average 13.5 years older than non-diabetic subjects (mean age ± SD: diabetic subjects: 60.9 ± 8.9; non-diabetic subjects: 47.4 ± 13.5).

Frequency of a positive parental history of diabetes (Table 1)

Overall, 13.1% of the participants had a diabetic mother, 7.2% had a diabetic father ($P = 0.001$), and 1.2% had two diabetic parents. Among diabetic subjects, 25.3% reported a maternal history and 10.9% reported a paternal history ($P = 0.001$). The respective numbers were 12.5% and 7.1% among those without diabetes ($P = 0.001$).

The frequency of a positive maternal and paternal history of diabetes decreased with increasing age of the subjects. This age effect was more pronounced for a paternal than for a maternal history of diabetes so that people with a positive paternal history of diabetes were considerably younger than people with a positive maternal history of diabetes (mean age ± SD: positive paternal history of diabetes: 45.0 ± 11.8; positive maternal history of diabetes: 49.4 ± 11.2).

Prevalence estimates of a positive parental history

Table 2 describes the frequency of a positive parental history of diabetes among diabetic and non-diabetic participants under different assumptions for subjects with an unknown parental status. It also shows the ratio of a positive maternal to paternal

Table 1 Frequency of an unknown and a positive parental history of diabetes by gender and age among diabetic and non-diabetic participants (total n = 12 751); pooled MONICA surveys 1984–1995

		Unknown[a]		Positive[b]	
Proband characteristics	**N**	Maternal history[c] %	Paternal history %	Maternal history[d] %	Paternal history %
All	12 751	8.8	17.3	13.1	7.2
Diabetic subjects	542	16.8	27.9	25.3	10.9
Gender[e]					
Female	240	15.4	25.0	30.0*	11.3
Male	302	17.9	30.1	21.5	10.6
Age (years)[f]					
<55	121	5.8†††	19.0†	31.4	21.5†††
⩾55	421	20.0	30.4	23.5	7.8
Non-diabetic subjects	12 209	8.4	16.8	12.5	7.1
Gender[e]					
Female	6181	6.5***	15.8**	13.3*	7.7**
Male	6028	10.4	17.9	11.8	6.4
Age (years)[f]					
<55	8102	5.6†††	14.4†††	13.2††	8.5†††
⩾55	4107	14.0	21.5	11.3	4.2

[a] History of diabetes was unknown for both parents in 4.8% of all subjects (non-diabetic subjects: 4.6%; diabetic subjects: 11.3%).

[b] History of diabetes was positive for both parents in 1.2% of all subjects (non-diabetic subjects: 1.1%; diabetic subjects: 3.3%).

[c] Mc Nemar's test for difference between an unknown maternal and paternal status of diabetes: *P*-value = 0.001 for all subgroups.

[d] Mc Nemar's test for difference between a positive maternal and paternal history of diabetes: *P*-value = 0.001 for all subgroups except diabetic subjects <55 years: *P* = 0.07.

[e] χ^2-test for difference between females and males: * *P*-value < 0.05, ** *P*-value < 0.01, *** *P*-value = 0.001.

[f] χ^2-test for difference between age groups: †*P*-value < 0.05, †† *P*-value < 0.01, ††† *P*-value = 0.001.

Table 2 Prevalence estimates of a positive maternal and paternal history of diabetes under different assumptions for subjects with unknown parental status of diabetes

	Unknown parental status assumed to be negative (0% +ive–100% –ive) (n = 12 751)	**Subjects with an unknown parental status excluded (n = 10 042)**	**Unknown parental status randomly distributed (40% +ive[a]–60% –ive) (n = 12 751)**	**Unknown parental status assumed to be positive (100% +ive–0% –ive) (n = 12 751)**
Diabetic subjects	n = 542	n = 361	n = 542	N=542
Maternal history	25.3%	29.4%	32.0%	42.1%
Paternal history	10.9%	16.1%	22.0%	38.7%
Ratio maternal history/paternal history	2.3	1.8	1.5	1.1
Non-diabetic subjects	n = 12 209	n = 9681	n = 12 209	N = 12 209
Maternal history	12.5%	13.3%	15.9%	21.0%
Paternal history	7.1%	8.4%	13.8%	23.9%
Ratio maternal history/paternal history	1.8	1.6	1.2	0.9

[a] The prevalence of a positive parental history among those who respond 'I don't know' (P) was estimated based on the adjusted OR obtained for the effect of a positive maternal/paternal history of diabetes and an unknown maternal/paternal history of diabetes in the logistic regression model (Table 3). According to a dose-response relationship between the logit transformed prevalence and the log OR, the prevalence P can be estimated by the ratio of the log OR for an unknown and a positive parental history. Since the OR for a maternal and paternal history of diabetes were quite similar, the mean OR were used and led to the prevalence estimate P = log 1.45/log 2.75 = 37%.

history. If people with an unknown parental status were included in the denominator but not in the numerator (i.e. they were assumed to have a negative parental history) results indicated that among diabetic subjects mothers were 2.3 times as likely to have diabetes as fathers. The respective ratio estimate was 1.8 among non-diabetic participants. When analyses were restricted to subjects with known parental history (i.e. those with a positive or negative parental history of diabetes) the prevalence ratio estimate of a maternal to paternal history was reduced to 1.8 and 1.6 among diabetic and non-diabetic subjects, respectively. Results obtained by this approach were very similar to the results obtained if people with an unknown parental status were randomly assigned either to the positive or negative parental history categories using the frequency of a positive maternal and paternal history observed in the data (results not shown). Under the assumption that the prevalence

Table 3 Odds ratios (OR) for the association between self-reported personal diabetes and a paternal and maternal history of diabetes from logistic regression models with various degrees of adjustment (n = 12 751)

	Not adj. for additional variables		**Adj. for age**		**Adj. for age, gender and survey**	
	OR	95% CI	OR	95% CI	OR	95% CI
Maternal history of diabetes						
Unknown versus negative	**2.2**	(1.7–2.9)	**1.4**	(1.1–1.8)	**1.3**	(1.0–1.8)
Positive versus negative	**2.7**	(2.2–3.3)	**2.8**	(2.3–3.5)	**2.9**	(2.3–3.6)
Paternal history of diabetes						
Unknown versus negative	**1.7**	(1.4–2.1)	**1.5**	(1.2–1.9)	**1.5**	(1.2–1.9)
Positive versus negative	**1.8**	(1.4–2.4)	**2.7**	(2.0–3.7)	**2.8**	(2.1–3.8)
Gender						
Female versus male	–	–	–	–	0.8	(0.6–0.9)
Age (continuous)						
1-year increase	–	–	1.10	(1.09–1.11)	1.10	(1.09–1.11)
Survey						
Survey 1 versus survey 3	–	–	–	–	1.1	(0.9–1.4)
Survey 2 versus survey 3	–	–	–	–	1.1	(0.9–1.4)

of a positive parental history is the same among people with an unknown maternal and an unknown paternal status of diabetes, the ratio is reduced further. If, for instance, it is assumed that 40% of subjects with unknown maternal and paternal status of diabetes in reality had a positive history, the ratio of a maternal history to a paternal history would be 1.5 and 1.2 among diabetic and non-diabetic participants, respectively.

Effect of a maternal and paternal history of diabetes when an unknown parental status is included in the model

Table 3 shows the OR for the association between personal diabetes and a maternal and paternal history of diabetes with various degrees of adjustment allowing for negative, unknown and positive parental history responses. A negative parental history was coded as the reference group and the maternal and paternal history variables were entered into the model simultaneously in order to adjust the effects for each other. The effect of a positive maternal history of diabetes was stronger than the effect of a positive paternal history of diabetes if the model was not adjusted for other covariables. However, adjustment for age considerably changed the OR and there was no longer a difference in the effect estimate of a positive maternal and a positive paternal history of diabetes. Further adjustment for gender and survey had only a marginal impact on the OR. A positive maternal history of diabetes was associated with a 2.9 times increased risk of diabetes while a positive paternal history was associated with a 2.8 times increased risk in the age-, gender- and survey-adjusted model. The OR were 1.3 and 1.5 for an unknown maternal and paternal status respectively. Results were very similar if variables for maternal and paternal history of diabetes were entered into separate models (data not shown).

There was no significant interaction between the effects of a maternal or a paternal history of diabetes and gender and between a maternal and paternal history of diabetes ($P = 0.15$ for maternal history * gender; $P = 0.21$ for paternal history * gender; $P = 0.21$ for maternal history * paternal history), therefore, only main effects are reported.

Effect of a maternal and paternal history of diabetes after exclusion of persons with an unknown parental status

When we excluded anyone with an unknown maternal or paternal status of diabetes, the OR for the association between a positive maternal and paternal history of diabetes with prevalent diabetes were very similar to the OR obtained for all participants. (Age-, survey- and gender-adjusted OR for a positive maternal history of diabetes: 2.8, 95% CI : 2.2–3.5; for a positive paternal history of diabetes: 3.0, 95% CI : 2.2–4.1).

Effect of a maternal and paternal history of diabetes after classifying 'I don't know' responses as 'negative'

When all those with an unknown parental status of diabetes were classified as 'negative', the OR for the association between a positive maternal and paternal history of diabetes and prevalent diabetes were reduced, but the effect estimates of a maternal and paternal history of diabetes were of still similar magnitude. (Age-, survey- and gender-adjusted OR for a positive maternal history of diabetes: 2.7, 95% CI : 2.2–3.3; for a positive paternal history of diabetes: 2.5, 95% CI : 1.9–3.4).

Discussion

The mode of inheritance of type 2 diabetes is still under discussion. Several studies have suggested marked excess maternal transmission[1–5,22] which has fuelled efforts to identify aetiological mechanisms consistent with these observations. These include mitochondrial inheritance paternal [6–8] genetic imprinting[9] and environmental mechanisms such as a diabetic intrauterine environment[10] and behavioural risk factors passed on preferentially by the mother.[11–13] Although, these mechanisms may be relevant in the transmission of diabetes mellitus, the excess of maternal transmission of diabetes may be much smaller than previously assumed. Our data show that the previously observed dominant maternal role can be partly explained by

several biases such as reporting bias, censoring bias or selection bias. Furthermore, we have demonstrated that the analysis strategy can have a significant impact on the conclusion concerning the transmission of diabetes.

In our data, as in most of the previous studies which concluded that there was marked excess maternal transmission of diabetes,[1,2,4,5] the frequency of a positive maternal history of diabetes was about twice as common as the frequency of a positive paternal history of diabetes when we ignored unknown parental status i.e. classified people with unknown parental status as 'negative'. However, *reporting bias* most likely contributed to the observed differences since unknown paternal status of diabetes was about twice as common as unknown maternal status of diabetes. Similar tendencies concerning differences between the frequency of an unknown maternal and paternal status of diabetes have been observed in two American studies.[22,23] We tried to quantify the impact of unknown parental status on the observed prevalences by randomly assigning either a positive or a negative parental history to those with unknown status. When we assumed that the percentage of parents with a true positive parental history was 40% among those with unknown maternal or paternal status the maternal excess was reduced. Although we cannot be sure that the prevalence of a positive parental history was the same among those with unknown maternal and those with unknown paternal status it seems relatively likely because the adjusted OR for the risk of diabetes were of similar magnitude for both groups compared to people with a negative history.

In addition to reporting bias, *censoring bias* most likely had an impact on the observed results as suggested earlier by Cox.[19] Age at death was considerably lower for fathers than for mothers (65.4 ± 14.9 years versus 69.4 ± 14.5 years, data not shown). Furthermore, the percentage of deceased fathers was significantly higher than the percentage of deceased mothers (66.0% versus 48.3%, data not shown). Males are more likely than women to die of cardiovascular disease (CVD) at an earlier age. Since type 2 diabetes, lipid abnormalities and CVD may have a common aetiological basis,[24] it seems likely that a higher percentage of fathers may have died before they developed clinically manifest diabetes mellitus.

Furthermore, the hypothesis that biases could explain the maternal transmission hypothesis is also supported by the observation that the difference in the frequency between a positive maternal and paternal history of diabetes was smaller in younger subjects. The biases described above were less likely to occur among younger people since an unknown parental status of diabetes was less common and fewer parents were deceased.

Finally, our results are supported by the fact that, in two studies in which parental history of diabetes was not only assessed by questionnaire but by medical examination of the parents,[14,15] the prevalence of a positive maternal and paternal history of diabetes was quite similar.

In extension to most previous studies our study comprised diabetic and non-diabetic participants. Therefore, it was possible to determine the frequencies of a positive maternal and paternal history of diabetes among non-diabetic subjects. Since the age-specific prevalence of diabetes was slightly higher among men than among women in our study population (data not shown) one would expect a similar or even higher frequency of a positive paternal than maternal history of diabetes among non-diabetic subjects if no biases influence the results. However, a positive maternal history of diabetes was also more common among non-diabetic participants. This is another indication that biases may have lead to an underestimation of a positive paternal history of diabetes.

One approach to reduce the impact of those biases which operate to a similar extent among diabetic and non-diabetic participants is the calculation of the OR as a measure of the relative risk. When we analysed our data with a multiple logistic regression model simultaneously entering a maternal and paternal history of diabetes, age, gender and survey into the model, we obtained OR which were quite similar for the effect of a positive maternal or paternal history of diabetes. The OR is defined as the ratio of the odds that the cases (i.e. people with diabetes) were exposed (i.e. had a positive parental history) to the odds that the controls (i.e. people without diabetes) were exposed. Therefore, biases which lead to an underestimation of the frequency of a positive paternal history of diabetes by a certain percentage among diabetic and among non-diabetic subjects will only marginally affect the OR even though the absolute percentages may be considerably lower. Few studies trying to quantify the impact of a maternal or paternal history of diabetes on the occurrence of diabetes have reported OR as the measure of effect presumably because most studies included only diabetic participants. In a Swedish study conducted in men aged 35–54 years[17] a maternal and a paternal history of diabetes were each associated with a 4.4 times higher risk of diabetes while the risk was 8.5 times higher if both parents had diabetes. For this analysis 27.4% of subjects with incomplete family history information had been excluded which may explain the relatively high OR. Mitchell *et al.*[25] also observed similar OR for a positive maternal and paternal history of diabetes among men, whereas an excess maternal effect was observed among women. An excess maternal transmission was also suggested by a Taiwanese study in which OR were calculated to quantify the effect.[3] However, this study was relatively small and there was a considerable overlap between the confidence intervals for the effect of a positive maternal and a positive paternal history of diabetes.

In summary, the results of our study demonstrate that different analytical approaches and classification schemes for parental history variables can lead to conflicting conclusions concerning excess maternal transmission of diabetes. Overall, our findings do not support a strong excess maternal role in the development of type 2 diabetes in the offspring. Future studies should assess the validity of reported parental history information and try to quantify the effect of potential biases in order to further clarify the pattern of transmission of type 2 diabetes.

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Contributors

Barbara Thorand devised the conceptual framework of the paper, conducted the analyses and wrote the manuscript. Hannelore Löwel participated in all parts of the study, as well as the interpretation of the data. Angela D Liese, Marie-Hélène Metzger and Peter Reitmeir were involved in the development of the analysis strategy, the interpretation of the data and the drafting of the paper. Andrea Schneider was responsible for the data management of the study and reviewed the analysis strategy. All the investigators contributed to the revisions of the manuscript.

KEY MESSAGES

- Unknown paternal status of diabetes was about twice as common as unknown maternal status.
- Analysis decisions concerning the classification of people with unknown parental status of diabetes can considerably influence the results concerning the transmission of diabetes.
- Odds ratios for the association between diabetes and self-reported maternal and paternal history of diabetes were strongly confounded by age of the subjects.
- The previously observed maternal excess in the transmission of diabetes can be partly explained by reporting and censoring bias.

References

[1] Alcolado JC, Alcolado R. Importance of maternal history of non-insulin dependent diabetic patients. *Br Med J* 1991;**302:**1178–80.

[2] Thomas F, Balkau B, Vauzelle KF, Papoz L, and the CODIAB-INSERM-ZENECA Study Group. Maternal effect and familial aggregation in NIDDM. The CODIAB Study. *Diabetes* 1994;**43:**63–67.

[3] Lin RS, Lee WC, Lee YT, Chou P, Fu CC. Maternal role in type 2 diabetes mellitus: indirect evidence for a mitochondrial inheritance. *Int J Epidemiol* 1994;**23:**886–90.

[4] Simmons D, Gatland BA, Leakehe L, Fleming C. Frequency of diabetes in family members of probands with non-insulin-dependent diabetes mellitus. *J Intern Med* 1995;**237:**315–21.

[5] Klein BE, Klein R, Moss SE, Cruickshanks KJ. Parental history of diabetes in a population-based study. *Diabetes Care* 1996;**19:**827–30.

[6] Alcolado JC, Thomas AW. Maternally inherited diabetes mellitus: the role of mitochondrial DNA defects. *Diabet Med* 1995;**12:**102–08.

[7] Gerbitz KD, van den Ouweland JM, Maassen JA, Jaksch M. Mitochondrial diabetes mellitus: a review. *Biochim Biophys Acta* 1995; **1271:**253–60.

[8] Rotig A, Bonnefont JP, Munnich A. Mitochondrial diabetes mellitus. *Diabetes Metab* 1996;**22:**291–98.

[9] Zemel S, Bartolomei MS, Tilghman SM. Physical linkage of two mammalian imprinted genes, H19 and insulin-like growth factor 2. *Nat Genet* 1992;**2:**61–65.

[10] Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM. Role of intrauterine environment. *Diabetes* 1988;**37:**622–28.

[11] Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;**35:**595–601.

[12] Mayer EJ, Newman B, Austin MA *et al*. Genetic and environmental influences on insulin levels and the insulin resistance syndrome: an analysis of women twins. *Am J Epidemiol* 1996;**143:**323–32.

[13] Warram JH, Rich SS, Krolewski AS. Epidemiology and genetics of diabetes mellitus. In: Kahn CR, Weir GC (eds). *Joslin's Diabetes Mellitus.* Philadelphia: Lea and Febinger, 1994, pp.201–15.

[14] Mitchell BD, Kammerer CM, Reinhart LJ, Stern MP, MacCluer JW. Is there an excess in maternal transmission of NIDDM? *Diabetologia* 1995;**38:**314–17.

[15] McCarthy M, Cassell P, Tran T *et al*. Evaluation of the importance of maternal history of diabetes and of mitochondrial variation in the development of NIDDM. *Diabet Med* 1996;**13:**420–28.

[16] Viswanathan M, McCarthy MI, Snehalatha C, Hitman GA, Ramachandran A. Familial aggregation of type 2 (non-insulin-dependent) diabetes mellitus in south India; absence of excess maternal transmission. *Diabet Med* 1996;**13:**232–37.

[17] Grill V, Persson G, Carlsson S *et al*. Family history of diabetes in middle-aged Swedish men is a gender unrelated factor which associates with insulinopenia in newly diagnosed diabetic subjects. *Diabetologia* 1999;**42:**15–23.

[18] Momiyama Y, Suzuki Y, Ohsuzu F, Atsumi Y, Matsuoka K, Kimura M. Maternally transmitted susceptibility to non-insulin-dependent diabetes mellitus and left ventricular hypertrophy. *J Am Coll Cardiol* 1999;**33:**1372–78.

[19] Cox NJ. Maternal component in NIDDM transmission. How large an effect? *Diabetes* 1994;**43:**166–68.

[20] Hense HW, Filipiak B, Döring A, Stieber J, Liese A, Keil U. Ten-year trends of cardiovascular risk factors in the MONICA Augsburg Region in Southern Germany. Results from the 1984/85, 1989/90 and 1994/1995 surveys. *CVD Prev* 1998;**1:**318–27.

[21] WHO MONICA Project Principal Investigators (prepared by H.Tunstall-Pedoe). The World Health Organization MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease): A major international collaboration. *J Clin Epidemiol* 1988;**34:** 105–14.

[22] Karter AJ, Rowell SE, Ackerson LM *et al*. Excess maternal transmission of type 2 diabetes. The Northern California Kaiser Permanente Diabetes Registry. *Diabetes Care* 1999;**22:**938–43.

[23] Burke GL, Savage PJ, Sprafka JM *et al*. Relation of risk factor levels in young adulthood to parental history of disease: The CARDIA study. *Circulation* 1991;**84:**1176–87.

[24] DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;**14:**173–94.

[25] Mitchell BD, Valdez R, Hazuda HP, Haffner SM, Monterrosa A, Stern HP. Differences in the prevalence of diabetes and impaired glucose tolerance according to maternal or paternal history of diabetes. *Diabetes Care* 1993;**16:**1262–67.