Biomarkers and prediction models for type 2 diabetes and diabetes related outcomes

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Chapter 5

Maternal and paternal transmission of type 2 diabetes: influence of diet, lifestyle and adiposity

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Abstract

Background Transmission of family history of type 2 diabetes to the next generation is stronger for maternal than paternal diabetes in some populations. The aim of the present study was to investigate whether this difference is explained by diet, lifestyle factors and/or adiposity.

Methods We analysed 35,174 participants from the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition, a prospective population-based cohort (aged 20–70 years) with a median follow-up of 10.2 years. Parental history of diabetes was self-reported. Occurrence of diabetes was mainly identified by self-report and verified by medical records.

Results Amongst 35,174 participants, 799 incident cases of diabetes were observed. In age-and sex-adjusted analyses, hazard ratio (HR) and 95% confidence intervals (CIs) for diabetes by maternal and paternal diabetes were 2.66 (2.26–3.14) and 2.40 (1.91–3.02), respectively. Maternal transmission of risk of diabetes was explained by diet (9.4%), lifestyle factors including smoking, alcohol consumption, physical activity and educational level (7.8%) and by adiposity, i.e. body mass index and waist and hip circumference (23.5%). For paternal transmission, the corresponding values were 2.9%, 0.0% and 9.6%. After adjustment for diet, lifestyle factors and adiposity, the HRs for maternal (2.20; 95%CI, 1.87–2.60) and paternal (2.23; 95% CI, 1.77–2.80) transmission of diabetes were comparable.

Conclusions Both maternal and paternal diabetes are associated with increased risk of type 2 diabetes, independently of diet, lifestyle and adiposity. The slightly higher risk conferred by maternal compared to paternal diabetes was explained by a larger contribution of diet, lifestyle factors and adiposity.

Introduction

The prevalence of type 2 diabetes, a leading cause of cardiovascular morbidity and mortality, is increasing worldwide[1]. Parental – paternal and/or maternal – history of diabetes is a major determinant of increased risk of diabetes[2-5]. Family history may reflect complex relationships between genetic factors and environmental conditions that are important for developing diabetes[6]. Thus, parental history of diabetes includes environmental risks (e.g. non-genetic familial behaviours, lifestyle and obesity) beyond the genetic risk factors for diabetes[4].

A greater risk from maternal type 2 diabetes compared to paternal diabetes has been reported in some[7-9] but not all studies [2,4,5]. A variety of explanations for this greater importance of maternal diabetes have included: genomic imprinting (ie the differential expression of inherited susceptibility genes in paternal or maternal generation[10]; mutations in mitochondrial DNA, which are maternally inherited[11]; and metabolic programming during intrauterine exposure[12]. It is still not clear to what extent modifiable factors such as diet, lifestyle and obesity can explain the association between maternal or paternal diabetes and risk of diabetes. To our knowledge, only one prospective study among female nurses has investigated the contribution of excess adiposity and certain dietary habits[5]. No such longitudinal data are available in men.

The aim of this study was to prospectively investigate the association between parental history of diabetes – maternal and/or paternal – and risk of incident type 2 diabetes in a population-based cohort of male and female adults, ie the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition (EPIC-NL). The EPIC-NL study was suitable for this purpose because detailed data on diabetes risk factors such as diet and lifestyle factors were collected in this cohort[13].

Methods

Study population and design

The EPIC-NL cohort (n=40,011) includes the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) and Prospect cohorts, initiated between 1993 and 1997. Details of the EPIC-NL study design, recruitment and procedures have been described in more detail previously[13]. Briefly, Prospect is a prospective population-based cohort study of 17,357 women aged 49–70 years who participated in a breast cancer screening programme. In the MORGEN study, 22,654 individuals aged 20–59 years were recruited from Amsterdam, Doetinchem and Maastricht. A new random sample of about 5000 participants was examined each year. These rounds of enrolment add up to this number of individuals. The participation rates were 34.5% for Prospect and 45.0% for MORGEN.

At baseline, a general questionnaire and a food frequency questionnaire (FFQ) were sent by post to all participants and these were returned after completion at the

medical examination. We excluded 1150 participants with missing data on baseline characteristics or extreme values for energy intake (<450 or >6000 kcal/day) and 2360 participants with unknown history of parental diabetes. Further subjects were excluded because of prevalent type 2 diabetes (n=507) or missing recordings of censoring time (n=820). Follow-up time was calculated from the date of enrolment to the date of diabetes diagnosis or death. All other participants were censored at the end of follow-up (January 2006). Finally, 35,174 participants were included in the cross-sectional and prospective analyses.

All participants gave written informed consent prior to study inclusion. Both cohort studies complied with the Declaration of Helsinki. Prospect was approved by the Institutional Review Board of the University Medical Center Utrecht and MORGEN was approved by the Medical Ethics Committee of the Netherlands Organization for Applied Scientific Research.

General measurements

The general questionnaire contained questions on demographic characteristics and risk factors for the presence of chronic diseases. For both cohorts, coding of this information was standardized and merged into one uniform database. Body weight, height and waist and hip circumference were measured according to standard procedures. Smoking status was categorized into current, past and never smoker. Physical activity was assessed using a questionnaire validated in an elderly population and categorized as inactive, moderately inactive, moderately active and active, according to the Cambridge Physical Activity Score[14]. Low education level was defined as primary education, lower vocational education or advanced elementary education. Blood pressure was measured twice on the left arm. The mean of the two blood pressure measurements was used in the analysis. In the Prospect study, systolic and diastolic blood pressures were measured with the participants in the supine position using a Boso Oscillomat (Bosch & Sohn, Jungingen, Germany), whereas a random-zero sphygmomanometer (Hawksley & Sons, Lancing, UK) with the participant in the sitting position was used in the MORGEN cohort. The comparability of these different measurement procedures has been described in more detail previously[15]. The assessment of the Prospect cohort slightly overestimated blood pressure compared with the MORGEN cohort. Hypertension was defined based on self-report of diagnosis by a physician, measured hypertension (≥140 mmHg systolic blood pressure or ≥90 mmHg diastolic blood pressure) or the use of blood pressure-lowering medication. Hyperlipidaemia was defined based on self-report of diagnosis by a physician or the use of lipid-lowering therapy.

In both cohorts, daily food intake was determined using the same validated FFQ[16,17], which contains questions on the usual frequency of consumption of 79 main food groups during the year preceding enrolment. Overall, the questionnaire enables estimation of the average daily consumption of 178 foods. Intakes of different nutrients were adjusted for total energy intake using the regression residual method[18].

Assessment of parental history of diabetes

Parental history of diabetes was obtained by self-report. Participants were asked whether their biological mother and/or father had (whether alive or deceased) previously been diagnosed with diabetes. Parental history of diabetes was categorized as none, any parent(s) (mother and/or father), maternal only, paternal only or both.

Assessment of type 2 diabetes

Occurrence of diabetes during follow-up was self-reported via two follow-up questionnaires at 3- to 5-year intervals in the MORGEN and Prospect studies. In the Prospect study, incident cases of diabetes were also detected as glucosuria via a urinary glucose strip test, which was sent out with the first follow-up questionnaire. Diagnoses of diabetes were also obtained from the Dutch Center for Health Care Information, which holds a standardized computerized register of hospital discharge diagnoses. Follow-up was complete until 1 January 2006. Potential cases identified by these methods were verified against general practitioner or pharmacist records (Prospect only) via postal questionnaires[19]. Diabetes was defined as being present when the diagnosis was confirmed by either of these methods. For 89% of participants with potential diabetes, verification information was available, and 72% were verified as having type 2 diabetes and were thus included in the analysis[19].

Statistical analyses

Baseline descriptive statistics of the continuous variables were reported as mean ± standard deviation (SD) and groups were compared using two-tailed Student's t-test or ANOVA. Categorical variables were presented as numbers and percentages and a χ^2 test was used to test the differences between participants without parental history of diabetes and those with each category of parental history of diabetes for these variables.

Generalized linear models were used to assess the cross-sectional associations between parental diabetes and baseline parameters of obesity, including body mass index (BMI) and waist and hip circumference in participants. Multivariable models were adjusted for cohort (Prospect or MORGEN), age, sex, lifestyle factors (smoking, alcohol consumption, physical activity level and educational level) total energy intake and energy-adjusted dietary factors. The dietary factors included the amount of intake of fat, protein, carbohydrate, cholesterol, fibre, vitamin C and vitamin E. The estimated marginal means and 95% confidence intervals (CIs) were reported and linear regression β coefficients and 95% CIs were calculated for each category of parental history of diabetes compared to the reference group of participants without any parental history of diabetes.

The association between parental history of diabetes and incident diabetes in participants was assessed by Cox proportional hazard regression. In the crude model (controlled for cohort), hazard ratios (HRs) and 95% CIs for diabetes were calculated for each category of parental diabetes against a reference group of participants

without parental history of diabetes. In Model 1, basic adjustments were made for age and sex. We assessed the effect of sex by including the interaction of sex with parental diabetes in this model. Moreover, the stratified analyses for sex were fitted in adjusted models for age and other covariates. Lifestyle factors were added in Model 2. Total energy intake and energy-adjusted dietary factors were added in Model 3. Parameters of obesity were subsequently included in the final model (Model 4). We then separately added each factor to Model 1 to determine its contribution to the association between parental history of diabetes and risk of diabetes. Inclusion of these factors in the model would be expected to attenuate the HR related to parental diabetes. We calculated the percentage attenuation of the HR for each category of parental diabetes. Percentage attenuation of HR was calculated as: (HR before addition–HR after addition)/(HR before addition–1)×100. A *P* value of 0.05 or less from two-sided tests was considered statistically significant. All statistical analyses were carried out using Statistical Package for Social Sciences version 16 (SPSS Inc, Chicago, IL, USA) and STATA software version 10.0 (Stata-Corp LP, College Station, TX, USA).

Results

Baseline characteristics of the study population are summarized in Table 1 by parental diabetes status. When compared with participants without parental history of diabetes, those who reported paternal and/or maternal diabetes were older and more likely to be female, had a higher BMI, waist and hip circumference and blood pressure, a lower alcohol consumption and education level, were less physically active, and were more likely to experience cardiovascular morbidity. Parental diabetes was associated with a lower intake of total energy and carbohydrates, whereas the intake of protein, fat, fibre, vitamin C and vitamin E was higher in participants with parental diabetes.

Cross-sectional analysis

Table 2 shows the association between parental history of diabetes and parameters of obesity in participants. We calculated adjusted means of parameters of obesity in each category of parental diabetes accounting for cohort, age, sex, diet and lifestyle factors. Subjects with maternal and/or paternal diabetes had higher BMI (β coefficient, 0.65; 95% CI, 0.55–0.75), waist circumference (β coefficient, 1.88; 95% CI, 1.62–2.15) and hip circumference (β coefficient, 0.93; 95% CI, 0.72–1.13) compared with participants without parental diabetes. This association was stronger for those with both maternal and paternal history of diabetes.

Prospective analysis

During a median follow-up of 10.2 years, we observed 799 incident cases of type 2 diabetes (rate of 2.2 per 1000 person-years). In the unadjusted analysis, participants with parental history of diabetes had an approximately 3-fold higher incidence rate of diabetes compared with those who had no parents with diabetes (Table 3; 1.7 vs. 5.0

Table 1. Baseline characteristics by parental history of diabetes in the EPIC-NL study (n=35,174) [a]

	None	Any parent(s)	Only father	Only mother	Both parents
No. (%) of participants	28,696 (81.6)	6478 (18.4)	2187 (6.2)	3941 (11.2)	350 (1.0)
Age, y	48.4 (12.3) [1,*]	51.6 (10.0)	49.7 (10.8) [2,*]	52.6 (9.4)	52.0 (9.7)
Female	21,026 (73.3) [1,*]	5148 (79.5)	1682 (76.9)	3178 (80.6)	288 (82.3)
Body mass index, kg/m^2	25.4 (3.9) [1,*]	26.4 (4.1)	26.0 (3.9) [2,*]	26.6 (4.2)	27.2 (4.6)
Waist circumference, cm	84.5 (11.2) [1,*]	86.8 (11.5)	85.8 (11.3) [2,*]	87.3 (11.6)	88.4 (12.0)
Hip circumference, cm	103.0 (7.9) [1,*]	104.7 (8.5)	103.9 (7.9) [2,*]	105.1 (8.7)	105.9 (9.7)
Systolic blood pressure, mmHg	125 (19) [1,*]	128 (19)	126 (19) [2,*]	130 (20)	128 (19)
Diastolic blood pressure, mmHg	77.4 (10.6) [1,*]	78.8 (10.4)	77.9 (10.6) [2,*]	79.4 (10.4)	78.2 (10.4)
Alcohol consumption, g/week	11.4 (15.6) [1,*]	9.9 (14.4)	10.6 (14.4)	9.7 (14.5)	7.9 (12.0)
Current smoker	8560 (29.8) [1,*]	1873 (28.9)	614 (28.1)	1171 (29.7)	88 (25.1)
Low educational level [b]	15,606 (54.4)	4229 (65.3)	1250 (57.2)	2734 (69.4)	245 (70.0)
Physical activity [c]	[1,**]				
Inactive	2450 (8.5)	626 (9.7)	185 (8.5)	402 (10.2)	39 (11.1)
Moderately inactive	8298 (28.9)	1837 (28.3)	649 (29.7)	1094 (27.8)	94 (26.9)
Moderately active	8045 (28.0)	1763 (27.2)	604 (27.6)	1049 (26.6)	110 (31.4)
Active	9903 (34.5)	2252 (34.8)	749 (34.2)	1396 (35.4)	107 (30.6)
Total energy intake, kcal/d	2076.6 (636.7) [1,*]	1992.3 (601.0)	2004.4 (604.8)	1991.4 (602.4)	1926.6 (556.9)
Nutrient intake, g/d [d]					
Protein	75.5 (10.9) [1,*]	76.7 (10.9)	76.0 (10.7) [2,**]	76.9 (11.0)	78.5 (11.7)
Fat	77.3 (11.3) [1,*]	78.4 (11.5)	78.0 (10.8)	78.5 (11.9)	79.1 (11.2)
Saturated fat	32.4 (5.8) [1,*]	33.0 (5.9)	32.6 (5.6) [2,**]	33.1 (6.0)	33.1 (5.6)
Monounsaturated fat	29.4 (5.1) [1,**]	29.6 (5.2)	29.6 (5.0)	29.6 (5.4)	29.9 (5.2)
Polyunsaturated fat	14.9 (3.8) [1,*]	15.1 (4.0)	15.1 (3.9)	15.1 (4.0)	15.5 (4.1)
Cholesterol, mg/d	215.9 (58.3) [1,*]	221.7 (62.6)	218.1 (59.3) [2,***]	221.9 (64.1)	230.7 (63.9)
Carbohydrates	222.3 (30.7)	220.8 (30.7)	221.2 (30.0)	220.6 (31.1)	220.7 (31.3)
Mono- and disaccharide	112.5 (29.3) [1,***]	111.7 (29.5)	111.2 (28.5)	112.1 (29.9)	110.5 (30.9)
Fibre	23.3 (4.8) [1,*]	23.7 (4.8)	23.4 (4.7) [2,***]	23.8 (4.8)	23.7 (4.6)
Vitamin C, mg/d	109.2 (45.1) [1,*]	111.6 (46.1)	110.1 (44.1)	112.4 (47.0)	112.7 (47.8)
Vitamin E, mg/d	12.2 (3.2) [1,*]	12.4 (3.3)	12.3 (3.3)	12.4 (3.3)	12.7 (3.5)
Hyperlipidaemia [e]	2268 (7.9) [1,*]	617 (9.5)	165 (7.5)	414 (10.5)	38 (10.9)
Hypertension [f]	5889 (20.5) [1,*]	1621 (25.0)	489 (22.4)	1023 (26.0)	109 (31.1)

Myocardial infarction	434 (1.5) [1,**]	121 (1.9)	28 (1.3)	82 (2.1)	11 (3.1)
Stroke	309 (1.1) [1,*]	101 (1.6)	26 (1.2)	65 (1.6)	10 (2.9)
Cancer	1187 (4.1)	264 (4.1)	80 (3.7)	171 (4.3)	13 (3.7)

[a] Data were given as mean (SD) for continuous variables, tested using two-tailed Student's t-test or ANOVA, and numbers (percentage) for categorical variables, tested using $\chi 2$ test.

[b] Low education level was assigned for participants who had primary education, lower vocational education or advanced elementary education.

[c] Physical activity level was defined based on the Cambridge Physical Activity Index.

[d] Intake of nutrients was adjusted for total energy intake and given in g/d unless otherwise indicated.

[e] Hyperlipidaemia was defined based on self-report of diagnosis by a physician or the use of lipid-lowering medications.

[f] Hypertension was defined based on self-report of diagnosis by a physician,, measured hypertension (>140 systolic blood pressure or >90 diastolic blood pressure) or the use of blood pressure-lowering medications.

[1] Comparisons between participants with any parental history of diabetes and none.

[2] Comparisons between participants with only paternal and only maternal history of diabetes.

*,$P<0.001$, **$P<0.01$ and ***$P\leq0.05$.

Table 2. Cross-sectional association between parental history of diabetes and BMI and waist and hip circumference (n=35,174)

Characteristics	None	Any parent(s)	Only father	Only mother	Both parents
Body mass index, kg/m^2					
Estimated means (95% CI) [a,b]	25.8 (25.7–25.8)	26.4 (26.3–26.5)	26.2 (26.0–26.3)	26.5 (26.4–26.7)	27.0 (26.6–27.3)
β coefficient (95% CI)	0	0.65 (0.55–0.75)	0.39 (0.23–0.55)	0.75 (0.63–0.88)	1.20 (0.81–1.56)
Waist circumference, cm					
Estimated means (95% CI) [a,b]	87.8 (87.7- 87.9)	89.7 (89.4–89.9)	89.1 (89.7–89.5)	89.9 (89.6–90.2)	90.9 (89.9- 91.9)
β coefficient (95% CI)	0	1.88 (1.62–2.15)	1.28 (0.86–1.70)	2.12 (1.79–2.44)	3.12 (2.10- 4.13)
Hip circumference, cm					
Estimated means (95% CI) [a,b]	102.9 (102.8- 103.1)	103.9 (103.7–104.1)	103.4 (103.1–103.8)	104.1 (103.8–104.3)	104.5 (103.7–105.3)
β coefficient (95% CI)	0	0.93 (0.72–1.13)	0.50 (0.17–0.83)	1.11 (0.86–1.37)	1.55 (0.75–2.35)

[a] Estimated marginal means (95% CI) were presented in generalized linear models adjusted for cohort, age, sex, smoking, alcohol use, physical activity levels, low educational level, total energy intake and nutrients (fat, protein, carbohydrate, cholesterol, vitamin C, vitamin E and fibre).
[b] $P<0.001$ for all comparisons between participants with any parental history of diabetes and none.

Table 3. Parental history of diabetes, contributing factors and risk of incident type 2 diabetes over 10 years (n=35,174)

		Risk of type 2 diabetes, HR (95% CI)			
Model adjustment	**None**	**Any parent(s)**	**Only father**	**Only mother**	**Both parents**
No. cases/participants	476/28696	323/6478	86/2187	201/3941	36/350
Incidence rate, per 1000 person-year	1.7	5.0	3.9	5.1	10.9
Crude model [a]	1 (ref)	2.90 (2.51–3.34)	2.36 (1.88–2.97)	2.91 (2.46–3.43)	6.21 (4.42–8.71)
Model 1	1 (ref.)	2.75 (2.39–3.17)	2.40 (1.91–3.02)	2.66 (2.26–3.14)	5.89 (4.20–8.27)
Model 2	1 (ref.)	2.64 (2.29–3.05)	2.40 (1.90–3.01)	2.53 (2.14–2.98)	5.49 (3.91–7.71)
Model 3	1 (ref.)	2.58 (2.24–2.97)	2.37 (1.88–2.98)	2.46 (2.09–2.91)	5.02 (3.57–7.06)
Model 4	1 (ref.)	2.32 (2.01–2.68)	2.23 (1.77–2.80)	2.20 (1.87–2.60)	3.92 (2.78–5.50)

[a] Crude model was controlled for cohort.

Model 1 was adjusted for age and sex.

Model 2 was adjusted for factors in Model 1 plus smoking status, alcohol consumption, physical activity levels and low educational level.

Model 3 was adjusted for factors in Model 2 plus total energy intake and energy-adjusted nutrients (fat, protein, carbohydrate, cholesterol, vitamin C, vitamin E and fibre).

Model 4 was adjusted for factors in Model 3 plus body mass index and waist and hip circumference.

per 1000 person-years, $P<0.001$). Despite the sex differences in each category of parental diabetes, there was no significant interaction of sex with parental diabetes (HR of interaction term, 0.86; 95% CI, 0.60–1.22). In sex-stratified analyses, multivariable-adjusted HRs of diabetes for maternal and paternal history of diabetes were 2.50 (95% CI, 1.72–3.62) and 2.14 (95% CI, 1.72–3.62), respectively, in male participants. In females, these values were 2.15 (95% CI, 1.79–2.6) and 2.32 (95%CI, 1.8–3.0), respectively.

In total, crude HRs of incident diabetes for maternal and paternal history of diabetes were 2.91 (95% CI, 2.46–3.43) and 2.36 (95% CI, 1.88–2.97), respectively, when compared with those who reported no parental diabetes. Model 1 in Table 3 shows that adjustment for age and sex modestly attenuated (13.1% reduction) the risk of diabetes by maternal diabetes (HR, 2.66; 95% CI, 2.26–3.14]), whereas this did not contribute to the risk conferred by paternal diabetes (HR, 2.40; 95% CI, 1.91–3.02). After multivariable adjustment (Model 4) for age, sex, diet, lifestyle factors and parameters of obesity, risk of diabetes was comparable for maternal (HR, 2.20; 95% CI, 1.87–2.60) and paternal history of diabetes (HR, 2.23; 95% CI, 1.77–2.80).

It is interesting that age, sex, diet, lifestyle factors and parameters of obesity contributed more to the association between maternal diabetes and risk of diabetes (overall attenuation of 37.1%) than paternal diabetes (overall attenuation of 9.6%). Therefore, we separately added each factor to Model 1 to assess its contribution to the association between category of parental diabetes and risk of diabetes. Parameters of obesity explained 23.5% and 9.6%, respectively, of the risk estimation of diabetes by maternal and paternal diabetes. Risk estimation of maternal diabetes was partly explained (9.4%) by energy intake and dietary determinants, whereas this accounted for only 2.9% of the association between paternal diabetes and risk of diabetes. After adjustment for lifestyle factors, an attenuation of 7.8% was observed in the association between maternal diabetes and risk of diabetes, whereas risk estimation of paternal diabetes was not affected by lifestyle factors.

Discussion

In this prospective cohort with over 10 years of follow-up, we found that both maternal and paternal history of diabetes were associated with baseline diabetes risk factors and with an increased risk of incident type 2 diabetes in participants, independent of diet, lifestyle and adiposity. However, the association between maternal diabetes history and risk of diabetes was slightly stronger in the age- and sex-adjusted model compared with paternal history. More than one-third of the maternal transmission of diabetes was explained by age, sex, diet, lifestyle factors (smoking status, alcohol consumption, physical activity and educational level) and parameters of obesity. The association between paternal diabetes and incident diabetes, however, was explained only modestly (~10%) by diet and parameters of obesity.

The main strengths of our study are its large sample size, prospective design, verification of incident diabetes and extensive information about participants' diet

and lifestyle factors. Nevertheless, our study has some limitations. The EPIC-NL cohort almost exclusively comprised Caucasians from the Netherlands, and it is unclear whether our findings could be extended to other ethnic groups. Another limitation is that parental history of diabetes was obtained by self-report which is the usual method in single-generation cohorts. Furthermore, we excluded individuals with missing data or unknown parental history of diabetes. Having unknown family history has been shown to be more common for paternal than for maternal diabetes[20]. However, the baseline characteristics of excluded individuals were similar to those who were included in our analysis. Therefore, it is unlikely that this would have led to recall bias or misclassification by category of parental diabetes of participants who did or did not develop diabetes. We relied on self-reported information about lifestyle and diet, which may be subject to misclassification. However, both the physical activity questionnaire and the FFQ have been validated previously[14,16,17]. These studies showed that both questionnaires could be used to rank individuals according to their physical activity or diet. We therefore believe that this did not greatly influence our results. Finally, individuals with type 2 diabetes may remain undiagnosed for several months to years and diagnosis of diabetes is always challenging in observational studies. Some cases of type 2 diabetes may have been undetected, resulting in underestimation of the association between parental diabetes and risk of diabetes in participants.

We first investigated the association between parental history of diabetes and baseline parameters of obesity in cross-sectional analyses. In multivariable-adjusted models, maternal or paternal diabetes was associated with higher BMI and waist and hip circumference. Having both maternal and paternal diabetes was associated with higher parameters of obesity. These findings are in agreement with those of other studies demonstrating that the presence of a maternal or paternal history of diabetes is associated with greater adiposity[21,22] and weight gain[23], thus suggesting that diabetes and obesity share some common heritable determinants[5,24].

A slightly more important role of maternal, compared with paternal, transmission of diabetes was shown in the present study in the age- and sex-adjusted model. This difference (~25%) was explained by diet and adiposity as well as age, sex and lifestyle factors for maternal diabetes. Of note, multivariable models have not been used to assess these factors in previous studies investigating the increased importance of maternal transmission[8,9,21]. Among these studies, adiposity substantially explained the risk of diabetes transmitted by maternal diabetes, whereas other factors contributed to a lesser extent.

In the present study, both maternal and paternal transmission of diabetes were explained to some extent by obesity parameters, with a 2-fold higher contribution for maternal than for paternal diabetes. The contribution of dietary determinants was also larger in the association between maternal diabetes and risk of diabetes when compared with paternal diabetes. In addition, the influence of age, sex and lifestyle factors was confined to the association between maternal diabetes and risk of diabetes. This finding was not observed in a recent analysis from the Nurses' Health

Study (NHS). In the NHS, BMI rather than waist and hip circumference largely explained the association between both maternal and paternal history of diabetes and risk of type 2 diabetes. In addition to BMI, it was suggested that a higher intake of red meat and sugar-sweetened beverages, and lack of alcohol consumption may explain part of the association between family history of diabetes and risk of diabetes[5]. Of interest, in our study, parental history of diabetes was related to a lower intake of total energy and carbohydrates but a higher energy-adjusted intake of fat, protein, fibre, vitamin C and vitamin E. These differences modestly explained the association between maternal diabetes and risk of diabetes, whereas the effect was minimal for paternal transmission. The NHS included a sample of female nurses with limited variation in socioeconomic status and with relatively healthy lifestyle behaviours. This selected sample may have led to an underestimation of the extent to which lifestyle factors explain parental transmission of diabetes[5].

The strong risk conferred by maternal or paternal diabetes was comparable after accounting for diet, lifestyle factors and adiposity. Of note, these factors differently explained maternal and paternal transmission of risk of diabetes. Our findings are consistent with previous evidence indicating a stronger magnitude of maternal transmission of obesity and its association with many lifestyle factors, compared with paternal transmission[25]. A possible explanation for this is that the mother might have more influence on eating habits and other lifestyle behaviours while raising her children. Indeed, there may be more contact hours between mothers and children during childhood and in later life, and therefore the mother's lifestyle may be more of an example for her children than the father's. It has been shown that if the mother has a history of diabetes during pregnancy, her child is less likely to follow certain healthy dietary recommendations[26]. Similarly, those with a maternal history of diabetes may be more prone to have an unhealthy diet and lifestyle throughout their lifetime. Finally, there is evidence to suggest an effect of maternal nutrition and weight maintenance during pregnancy on infant birth weight[27,28]. Birth weight could in turn influence future risk of chronic diseases such as type 2 diabetes[29,30].

Diabetes is a polygenic disease in which multiple genetic and environmental components play roles throughout all stages of the disease[6,31]. Beyond the genetic heritability, parental history of diabetes also carries environmental risk factors. In other words, it seems that parents and children share common lifestyle behaviours which will be continued throughout the children's lifetime. These components, transmitted by maternal or paternal exposures, may explain the heterogeneity of diabetes transmission in different populations.

We conclude that both maternal and paternal history of diabetes are associated with an increased risk of developing type 2 diabetes, independent of diet, lifestyle and adiposity. The slight excess risk conferred by maternal compared to paternal diabetes is explained by a larger contribution to this association of age, sex, diet, lifestyle factors and adiposity.

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References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-53
2. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. Diabetes 2000; 49: 2201-7
3. Wilson PW, Meigs JB, Sullivan L, Fox CS, NathanDM, D'Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med 2007; 167:1068–74
4. Meigs JB, Shrader P, Sullivan LM, et al. Genotype Score in Addition to Common Risk Factors for Prediction of Type 2 Diabetes. N Engl J Med 2008; 359: 2208-19
5. van 't Riet E, Dekker JM, Sun Q, Nijpels G, Hu FB, van Dam RM. The role of adiposity and lifestyle in the relationship between family history of diabetes and 20-year incidence of type 2 diabetes in U.S. women. Diabetes Care 2010 doi: 10.2337/dc09-1586
6. Grarup N, Andersen G. (2007) Gene-environment interactions in the pathogenesis of type 2 diabetes and metabolism.Curr Opin Clin Nutr Metab Care 2007; 10:420-26
7. Vaag A, Lehtovirta M, Thye-Rönn P, Groop L; European Group of Insulin Resistance. Metabolic impact of a family history of Type 2 diabetes. Results from a European multicentre study (EGIR). Diabet Med 2001; 18: 533-40
8. 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
9. Groop L, Forsblom C, Lehtovirta M, et al. Metabolic consequences of a family history of NIDDM (The Botnia Study): evidence for sex-specific parental effects. Diabetes 1996; 45: 1585-93
10. Rampersaud E, Mitchell BD, Naj AC, Pollin TI. Investigating parent of origin effects in studies of type 2 diabetes and obesity. Curr Diabetes Rev 2008; 4: 329-39
11. Maassen JA, Janssen GM, t Hart LM. Molecular mechanisms of mitochondrial diabetes (MIDD). Ann Med 2005; 37: 213-21
12. Fetita LS, Sobngwi E, Serradas P, Calvo F, Gautier JF. Consequences of fetal exposure to maternal diabetes in offspring, J Clin Endocrinol Metab 2006; 91: 3718-24
13. Beulens JW, Monninkhof EM, Verschuren WM. Cohort profile: The EPIC-NL study. Int J Epidemiol 2009 doi:10.1093/ije/dyp217
14. Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. Med Sci Sports Exerc 1991; 23: 974-9
15. Schulze MB, Kroke A, Saracci R, Boeing H. The effect of differences in measurement procedure on the comparability of blood pressure estimates in multi-centre studies. Blood Press Monit 2002; 7: 95-104
16. Ocké MC, Bueno-de-Mesquita HB, Goddijn HE, et al. The Dutch EPIC Food Frequency Questionnaire. I. Description of the questionnaire, and relative validity and reproducibility for food groups. Int J Epidemiol 1997; 26: S37-S48
17. Ocké MC, Bueno-de-Mesquita HB, Pols MA, Smit HA, van Staveren WA, Kromhout D. The Dutch EPIC Food Frequency Questionnaire. II. Relative validity and reproducibility for nutrients. Int J Epidemiol 1997; 26: S49-S58
18. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr 2004; 80: 348-56
19. Sluijs I, van der A DL, Beulens JW, et al Ascertainment and verification of diabetes in the EPIC-NL study. Neth J Med 2010; 68:333-9
20. Thorand B, Liese AD, Metzger MH, Reitmeir P, Schneider A, Löwel H. Can inaccuracy of reported parental history of diabetes explain the maternal transmission hypothesis for diabetes? Int J Epidemiol 2001; 30:1084-9

21. Lee SC, Pu YB, Chow CC, et al. Diabetes in Hong Kong Chinese: evidence for familial clustering and parental effects, Diabetes Care 2000; 23: 1365-8
22. Shaw JT, Purdie DM, Neil HA, Levy JC, Turner RC. The relative risks of hyperglycaemia, obesity and dyslipidaemia in the relatives of patients with Type II diabetes mellitus. Diabetologia 1999; 42: 24-7
23. Samocha-Bonet D, Campbell LV, Viardot A, et al. A family history of type 2 diabetes increases risk factors associated with overfeeding. Diabetologia 2010; 53: 1700-8
24. Rice T, Bouchard C, Perusse L, Rao DC. Familial clustering of multiple measures of adiposity and fat distribution in the Quebec Family Study: a trivariate analysis of percent body fat, body mass index, and trunk-to-extremity skin fold ratio. Int J Obes Relat Metab Disord 1995;19: 902-8.
25. Cooper R, Hyppönen E, Berry D, Power C. Associations between parental and offspring adiposity up to midlife: the contribution of adult lifestyle factors in the 1958 British Birth Cohort Study. Am J Clin Nutr 2010 doi: 10.3945/ajcn.2010.29477
26. Kvehaugen AS, Andersen LF, Staff AC. Dietary intake and physical activity in women and offspring after pregnancies complicated by preeclampsia or diabetes mellitus. Acta Obstet Gynecol Scand 2010;89:1486-90
27. Pirkola J, Pouta A, Bloigu A, et al. Risks of overweight and abdominal obesity at age 16 years associated with prenatal exposures to maternal prepregnancy overweight and gestational diabetes mellitus. Diabetes Care 2010; 33:1115-21
28. Steyn NP, Mann J, Bennett PH, et al. Diet, nutrition and the prevention of type 2 diabetes. Public Health Nutr 2004;7:147-65
29. Eriksson JG, Osmond C, Kajantie E, Forsén TJ, Barker DJ. Patterns of growth among children who later develop type 2 diabetes or its risk factors. Diabetologia 2006;49:2853-8
30. Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic review. JAMA 2008;300:2886-97
31. Bruce DG, Van Minnen K, Davis WA, et al. Maternal family history of diabetes is associated with a reduced risk of cardiovascular disease in women with type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care 2010; 33:1477-83

Chapter 5a

Commentary: Both multiplicative and additive components may contribute to parental transmission of type 2 diabetes – a response to K. Hemminki and X. Li and J. Sundquist and K. Sundquist

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Dear Sir,

We thank Hemminki and coworkers for their interest in our recent findings concerning parental transmission of type 2 diabetes [1]. Based on their and our data [1,2], they concluded that paternal and maternal history of diabetes simply add rather than act multiplicatively to increase risk for diabetes in offspring. They do so because in the Swedish model a fully multiplicative model was rejected on statistical grounds. We agree that based on these data it is very unlikely that paternal and maternal transmission of diabetes act in an entirely multiplicative manner. However, both in their and our study, the relative risk predicted by an additive model (3.7 for their study and 3.4 for our study) is lower than the actually observed risk (4.3 for their study and 3.9 for our study). Earlier findings were also consistent with these results, with relative risks of 3.6 in Pima Indians and 5.9 Framingham Offspring predicted by an additive model, while actually observed risks were higher, with values of 3.9 and 6.1 respectively [3,4] Thus, data of all 4 studies to date are in the same direction, with a higher actually observed risk in subjects with two affected parents than predicted by an additive model. Therefore, given that a multiplicative model does not fit the data, acceptance of an additive model as sole valid alternative seems an oversimplification, with the truth lying in between both of these extremes. It is important to acknowledge the possibility of non-additive genetic effects (epistasis or gene-gene interactions) of individual loci playing a role in transmission of risk of type 2 diabetes, because this is considered a source of missing heritability in complex diseases, including type 2 diabetes [5]. As many low-penetrance loci may contribute to genetic susceptibility for type 2 diabetes [6], such a scenario does not seem unrealistic.

References

1. Abbasi A, Corpeleijn E, van der Schouw YT, et al. Maternal and paternal transmission of type 2 diabetes: influence of diet, lifestyle and adiposity. J Intern Med 2011; doi: 10.1111/j.1365-2796.2011.02347.x.
2. Hemminki K, Li X, Sundquist K, Sundquist J. Familial risks for type 2 diabetes in Sweden. Diabetes Care 2010;33:293–7.
3. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. Am J Epidemiol 1981;113:144–56.
4. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. Diabetes 2000;49:2201-7.
5. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461:747–53.
6. Salanti G, Southam L, Altshuler D, et al. Underlying genetic models of inheritance in established type 2 diabetes associations. Am J Epidemiol 2009;170:537–45.