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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

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ABSTRACT

Objective

To evaluate to what extent the association between family history of diabetes and risk of type 2 diabetes can be explained by excess adiposity and lifestyle risk factors.

Research design and methods

We analyzed data from 73,227 women who participated in the Nurses' Health Study cohort. A family history of diabetes was defined as having at least one first degree family member with diabetes. Lifestyle factors, weight and height were assessed by using validated questionnaires, and body mass index (BMI) was calculated. The relative risk of type 2 diabetes was estimated using Cox proportional hazards analysis.

Results

We documented 5101 cases of type 2 diabetes during 20 years of follow-up. The age-adjusted relative risk of type 2 diabetes in participants with a family history was 2.27 (95% CI 2.14-2.40) as compared with those without a family history of diabetes. Participants with a family history of diabetes had a higher BMI and were more likely to have a parental history of obesity. BMI explained 21.1% (95% CI 19.4-22.9) of the association between family history of diabetes and risk of type 2 diabetes. Intakes of red meat, alcohol and sugar-sweetened beverages explained 1.1% (95% CI 0.8-1.3), 4.8% (95% CI 4.3-5.3) and 2.8% (95% CI 2.4-3.2) of this association respectively.

Conclusions

These results suggest that excess adiposity and, to a lesser extent, specific dietary habits can explain a substantial part of the association between having a family history of diabetes and risk of type 2 diabetes.

INTRODUCTION

One of the major risk factors for type 2 diabetes is a positive family history of diabetes. In prospective studies, a family history of diabetes has consistently been associated with a higher risk of type 2 diabetes (1,2), but the reason for this association remains largely unknown. Recent studies have shown that currently identified genetic risk variants do not explain a substantial part of this association between family history of diabetes and risk of type 2 diabetes (3,4). In the Framingham Heart Study, adjusting a score based on 18 identified genetic risk variants reduced the relative risk of type 2 diabetes for having parental history of diabetes from 2.26 to 2.16 (3).

The clustering of body fatness in families, which can be due to both shared genetic and shared environmental influences, may also contribute to the relationship between family history and the development of type 2 diabetes. In cross-sectional studies, greater generalized adiposity, rather than an abdominal fat distribution, was observed in persons with a family history of diabetes than in those without a positive family history (5-7). However, the contribution of lifestyle risk factors and excess adiposity to the association between family history of diabetes and risk of type 2 diabetes has not been examined in prospective studies. In addition, the relative contribution of a family history of obesity and a family history of diabetes to the risk of type 2 diabetes has not been previously evaluated. Therefore, we prospectively evaluated the following hypothesis in the Nurses' Health Study: 1). a large proportion of the association between family history of diabetes and risk of type 2 diabetes can be explained by greater generalized adiposity 2). To a lesser extent, specific lifestyle factors can explain part of the association between family history of diabetes and risk of type 2 diabetes. 3) A family history of obesity is associated with a higher risk of type 2 diabetes independent of a family history of diabetes.

METHODS

Study design and population for analysis

The Nurses' Health Study (NHS) was started in 1976 when 121,700 married female registered nurses aged 30-55 years received a questionnaire on health status and potential risk factors for major chronic diseases. Ever since, participants were sent questionnaires biennially and the response rates have been approximately 90% (8). The NHS was approved by the institutional review board of the Brigham and Women's Hospital (Boston, MA).

For the present analysis, we used the return of the 1984 questionnaire, which was completed by 97,510 participants, as baseline because information for family history was first collected in 1982 and the first extended food frequency questionnaire (FFQ) was administered in 1984. In this 1984 questionnaire, complete dietary information was available for 81,757 women. Women with a history of type 2 diabetes at baseline (N=329) were excluded. Furthermore, we excluded participants with cancer (except for non-melanoma skin cancer) or cardiovascular diseases at baseline (N= 4934), because the diagnosis of these diseases could have interfered with self-reports of lifestyle and family history. Women with incident types of diabetes other then type 2 diabetes or unconfirmed type 2 diabetes were also excluded (N=1480). Moreover, women with missing information for diabetes status, family history of diabetes, date of birth, weight or height were excluded (N=1787). As a result, 73,227 women remained for the present analysis. There were no differences between the total study population (N=81,757) and the population included for this analysis (N=73,227) for baseline characteristics, except for slight differences in mean (SD) age [50.6 (7.21) and 50.2 (7.17) years], the proportion of participants with obesity (13.3% and 12.3%), weight change since age 18 years [28.3 (38.0) and 27.6 (37.4) kg] and the proportion of participants reporting to drink no alcohol (31.5% and 30.6%) or over 10 grams of alcohol a day (23.6% and 24.0%).

Assessment of family history of diabetes and parental body size

Women were asked to report if any of their first degree family members (father, mother and/or siblings) ever had diabetes in the questionnaires mailed in 1982, 1988 and 1992. No questions about the type of diabetes in family members were included.

To assess obesity in the parents, a series of pictograms of body shape were included in the 1988 questionnaire (9). The pictograms estimate relative obesity, with values ranging from one (very thin) to nine (very obese). Women were asked to choose the pictogram that best described the body shape of their natural mother and their natural father at age 50 years. Previous research has shown that these pictograms can provide a reasonably accurate estimate of measured BMI of the parents 15 years in the past (r=0.74 for mothers and 0.63 for fathers) (9). According to the chosen image, both father and mother were categorized as non-obese (image 1-5) or obese (image 6-9).

Assessment of lifestyle, socio-economic status, race and adiposity

Dietary information was collected using a semi-quantitative FFQ included in the questionnaires mailed to the participants in 1984, 1986, 1990, 1994, 1998 and 2002. The reported portions were converted to gram weights per serving, and intakes of nutrients were computed by multiplying the frequency of consumption by the nutrient content in grams. The FFQ has been validated against biomarkers and diet records (10,11). Physical activity was assessed every 2 to 4 years asking about the time spent on vigorous and moderate physical activity on an average day in the last month. Information on cigarette smoking was assessed every 2 years. Information on the highest educational degree of the participant and their husband, father and mother's occupation and race were assessed in the 1992 questionnaire.

Height was assessed in the baseline questionnaire and body weight every 2 years. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared (kg/m^2). In 1980, women were asked to

report their weight at age 18 years, which we used to calculate BMI at age 18 and weight change since age 18. In 1986, 1996 and 2000, waist circumference was assessed by questionnaires that included measurement instructions and a tape measure. The validity of self-reported weight and circumference measurements was assessed in 140 participants from the Nurses' Health Study aged 41-65 years. The self-reported data were compared with the average of two standardized measurements taken approximately six months apart by technicians who visited participants at their homes. Pearson correlations between self-reported and technician-measured weight, waist circumference and hip circumference were high (r=0.97, 0.89 and 0.84 respectively), indicating that self-reported measures in this population are reasonable valid (12).

Ascertainment of type 2 diabetes

Women who reported to have diabetes in the biennial questionnaires were mailed a supplemental questionnaire to receive more information on diagnosis and treatment. The National Diabetes Data Group criteria (13) were used to confirm diagnosis of diabetes according to 1). an elevated glucose concentration (fasting plasma glucose of ≥7.8 mmol/l, random plasma glucose of ≥11.1 mmol/l, or plasma glucose ≥11.1 mmol/l after an oral glucose load), and at least one symptom related to diabetes (excessive thirst, polyuria, weight loss, or hunger); 2). no symptoms, but elevated glucose concentrations on two occasions; or 3). treatment with insulin or oral hypoglycemic medication. For cases of type 2 diabetes identified after 1998, the American Diabetes Association criteria (14) were used, lowering the cut-off point for fasting plasma glucose concentrations to 7.0 mmol/l. In a subsample, type 2 diabetes which was confirmed by the supplementary questionnaire was consistent with medical record reviews by an endocrinologist in 98% of the cases (15).

Statistical analysis

Differences in baseline characteristics between participants with and without a family history were analyzed using Chi-square test for categorical variables and Student's t-tests for continuous variables.

Person-time for each participant was calculated from the date of return of the 1984 questionnaire to the date of diagnosis of type 2 diabetes, death, or June 2004, whichever came first. Cox proportional hazard analysis was used to estimate the relative risk for type 2 diabetes according to family history. To evaluate the contribution of different covariates on the association between family history and diabetes risk, we used multivariate models with the following adjustments: 1). Age. 2). Age, socio-economic status (SES; occupation of the father, occupation of the mother, husband's highest degree, and participants highest degree) and race. 3). Age, SES, race, and lifestyle (smoking, physical activity, polyunsaturated-to-saturated fat intake ratio and intakes of coffee, alcohol, fruit, vegetables, sugar-sweetened beverages, whole grains, red meat, *trans*-fat, and total energy). 4). Age, SES, race, lifestyle, and BMI. Additional analyses were performed to evaluate whether inclusion of waist circumference or a combination of BMI at age 18 and weight change since age 18 in the statistical model (as continuous variables) would alter the results. In addition, we conducted a sensitivity analysis evaluating the effect of blood glucose testing on the results. Since 1998, women were asked biennially to report whether they had been screened for fasting blood glucose in the previous two years. We repeated our analysis for follow-up cycles from 1996 to 2004 restricted to women who reported to have been tested for blood glucose during a 2-year follow-up period.

All covariates were updated during follow-up whenever new information was obtained. For example, BMI in 1984 was used for the follow-up from 1984 to 1986 and BMI in 1986 was used for follow-up from 1986 to 1988. For dietary variables we used cumulative updating to reduce within-person variation (16).

The proportion of the association explained by including different covariates into the model was calculated based on the change in regression coefficients, using the method by Lin et al. (17) to calculate the 95% confidence intervals.

All P-values were two tailed, and values less than 0.05 were considered statistically significant. Inclusion of multiplicative interaction terms between time and family history in the multivariate models suggested that the proportional hazard assumption was not violated. The SAS statistical program version 9.1 (SAS Institute Inc., Cary, North Carolina) was used for all analyses.

Online Appendix Table A1. Baseline characteristics according to family history of diabetes

	No family history	Family history
N (%)	59,395 (81)	13,832 (19)
Age (years)	50.1 (7.2)	50.7 (7.0)
Body mass index (kg/m^2)	24.7 (4.5)	25.5 (4.9)
Body mass index: 25-30 kg/m^2 (%)	25.6	29.4
Body mass index: ≥ 30 kg/m^2 (%)	11.5	15.6
Body mass index at age 18 (kg/m^2)	21.2 (2.8)	21.6 (3.2)
Weight change since age 18 (lbs)	27.5 (38.1)	27.7 (34.3)
Waist (inches)	30.7 (4.2)	31.5 (4.4)
Body size parents: mother obese (%)	27.8	42.3
Body size parents: father obese (%)	16.8	26.3
Smoking: never smoker (%)	43.6	45.3
Smoking: past smoker (%)	31.7	32.2
Smoking: current smoker (%)	24.7	22.5
Physical activity (hours/week)*	3.2 (2.1)	3.1 (2.1)
Coffee consumption (cups/day)	2.4 (1.8)	2.4 (1.8)
Alcohol consumption (g/day)	7.2 (11.4)	6.1 (10.5)
Alcohol consumption: 0 g/day (%)	29.9	33.7
Alcohol consumption: 0.1-4.9 g/day (%)	33.4	34.7
Alcohol consumption: 5.0-9.9 g/day (%)	11.9	11.4
Alcohol consumption: ≥ 10 g/day (%)	24.9	20.2
Whole grain intake (g/day)	14.0 (13.1)	13.9 (12.8)
Red meat intake (servings/day)	1.1 (0.7)	1.2 (0.7)
Red meat intake: > 1 serving/day (%)	51.4	53.4
Fruit intake (servings/day)	2.1 (1.4)	2.2 (1.4)
Vegetable intake (servings/day)	3.1 (1.6)	3.1 (1.7)
Sugar-sweetened beverage intake (servings/day)	0.80 (1.1)	0.83 (1.1)
Trans-fat intake (g/day)	3.4 (1.1)	3.4 (1.1)
P:S ratio	0.6 (0.2)	1.6 (0.2)
Race: non-white (%)	5.3	6.0
Occupation father: none (incl. retired, deceased) (%)	10.0	7.8
Occupation father: craftsmen/laborer/farmer (%)	26.0	24.1
Occupation father: clerical/sales/services (%)	38.4	38.7
Occupation father: professional/managerial (%)	25.5	29.3
Occupation mother: none (incl. retired, deceased) (%)	5.7	3.9
Occupation mother: housewife (%)	63.7	68.0
Occupation mother: craftsmen/laborer/farmer (%)	5.9	6.2
Occupation mother: clerical/sales/services (%)	16.0	14.2
Occupation mother: professional/managerial (%)	8.8	7.8
Husband's degree: < high school (%)	1.8	2.2
Husband's degree: high school (%)	43.0	47.5
Husband's degree: college graduated (%)	29.9	28.1
Husband's degree: graduate school (%)	25.4	22.2
Participant's degree: registered nurse (%)	69.1	71.3
Participant's degree: bachelors degree (%)	20.8	18.4
Participant's degree: university degree (%)	10.1	10.3

Data are presented as mean (SD) or percentage. A family history of diabetes denotes diabetes in one or more first-degree family members. P:S ratio denotes dietary polyunsatured to saturated fat ratio. Differences between the 2 groups in all variables were significant with p <0.001, except for coffee consumption (p=0.52), fruit intake (p=0.16) and P:S ratio (p=0.01).

** Physical activity of moderate-to-vigorous intensity*

RESULTS

We documented 5101 cases of incident type 2 diabetes during 1,365,617 person-years of follow-up. In women without and with a family history of diabetes, the incidences of type 2 diabetes were 26 and 68 per 10,000 person-years respectively.

Baseline characteristics

Online Appendix Table A1 presents the baseline characteristics of the 73,227 participants according to family history of diabetes. As compared with participants without a family history, participants with a family history were slightly older, had a higher BMI and waist circumference, were more likely to have parents with obesity, and had a lower alcohol intake and a higher intake of red meat and sugar-sweetened beverages.

Family history, lifestyle and adiposity, and risk of type 2 diabetes

Table 1 presents the risk of type 2 diabetes in different categories of a family history of diabetes. After adjusting for age, the relative risk of type 2 diabetes in participants with a family history was 2.27 (95% confidence interval [CI] 2.14-2.40) as compared with participants without a family history. The relative risk of type 2 diabetes was similar for having a maternal or paternal history of diabetes.

We evaluated whether various diabetes risk factors could explain the association between family history and risk of type 2 diabetes. Adjustment for socio-economic status and race did not substantially change the association between family history and diabetes risk, whereas adjustment for lifestyle explained part of the association (Table 1). To further evaluate this, we included all factors separately into the model. Consumption of alcohol, red meat and sugar-sweetened beverages explained 4.8% (95% CI 4.3-5.3), 1.1% (95% CI 0.8-

1.3) and 2.8 (95% CI 2.4-3.2) respectively of the association between family history of diabetes and risk of type 2 diabetes, whereas other lifestyle variables did not significantly contribute to explaining the association. Adjustment for BMI also weakened the association between family history of diabetes and risk of type 2 diabetes (Table 1) explaining 21.1% (95% CI 19.4-22.9) of the association. Adding BMI into the models with alcohol, red meat and sugar-sweetened beverages, lowered the percentages explained of alcohol, red meat and sugar-sweetened beverages to 2.3% (95% CI 1.9-2.8), 0.3% (95% CI 0.2-0.5) and 0.7% (95% CI 0.4-1.0) respectively.

We conducted a sensitivity analysis restricted to women who underwent blood glucose screening for the 1996 to 2004 period in which this information was available. In this period, the age-adjusted relative risk of type 2 diabetes for having a family history of diabetes was slightly weaker for women who were screened (RR 1.97; 95% CI 1.82-2.13) as compared with the complete study population (RR 2.21; 95% CI 2.05-2.38). However, among the screened women the effect of additionally adjusting for SES and race, lifestyle, and adiposity was essentially the same as for the complete study population (Online Appendix Table A2).

To further explore the role of adiposity in the association between a family history of diabetes and incident diabetes, we ran various models adjusting for waist and hip circumference or adolescent BMI and adult weight change (Table 2). Neither considering measures of body fat distribution nor adolescent BMI explained a substantially greater proportion of the association between family history and diabetes risk as compared with the model that only included BMI.

Table 1. Relative risk of type 2 diabetes according to family history of diabetes during 20 year follow-up (1984-2004)

	No family history	Family history	Father only	Mother only	Sibling only	> 1 family member
Number of cases	3132	1969	517	727	240	485
Person-years	1,075,728	289,889	90,785	111,880	42,423	44,800
Adjusted relative risks (95% CI)						
Age [1]	1 (ref.)	2.27 (2.14-2.40)	2.04 (1.86-2.24)	2.18 (2.01-2.36)	1.72 (1.51-1.97)	3.42 (3.11-3.77)
SES/ race [2]	1 (ref.)	2.26 (2.13-2.39)	2.08 (1.89-2.29)	2.16 (1.99-2.35)	1.69 (1.48-1.93)	3.36 (3.05-3.71)
Lifestyle [3]	1 (ref.)	2.13 (2.01-2.26)	1.97 (1.79-2.16)	2.05 (1.89-2.22)	1.64 (1.44-1.88)	3.06 (2.77-3.37)
BMI [4]	1 (ref.)	1.91 (1.80-2.02)	1.78 (1.61-1.95)	1.85 (1.70-2.01)	1.47 (1.29-1.69)	2.62 (2.37-2.89)

95% CI denotes 95% confidence interval; BMI denotes body mass index; SES denotes socio-economic status. A family history of diabetes denotes diabetes in one or more first-degree family members.

[1] *Adjusted for age (continuous in months)*

[2] *Model 1 additionally adjusted for occupation father (none, professional/managerial, clerical/sales/services), occupation mother (none; professional/managerial; clerical/sales/services), husband's highest degree (< high school, some HS, HS gad, college grad, grad school), participants highest degree (registered nurse, bachelor, master, doctoral), race (white, black, Asian, other)*

[3] *Model 2 additionally adjusted for smoking (never, past, current smokers: ≤ 14, 15-24, ≥ 25 cigs/day), physical activity (<1.0, 1.0-1.9, 2.0-3.9, 4.0-6.9, ≥ 7.0 hours/week), intake of coffee (0, 0.1-0.9, 1.0-1.9, 2.0-3.9, 4.0-5.9, ≥ 6 cups/day), alcohol (0, 0.1-4.9, 5.0-9.9, ≥ 10.0 g/day), fruit (quintiles), vegetables (quintiles), sugar-sweetened beverages (quintiles), whole grain (quintiles), red meat (quintiles), trans-fat (quintiles), total energy (quintiles), and polyunsatured-to-saturated fat ratio (quintiles)*

[4] *Model 3 additionally adjusted for BMI (<21, 21-23, 23-25,25-27,27-30,30-33,33-35,35-40,>40 kg/m^2)*

Table 2. Relative risk of type 2 diabetes according to family history of diabetes adjusted for various measures of body fatness

	No family history	Family history
Adjustment for adolescent BMI (1984-2004)[1]		
Model 1[2]	1 (ref.)	2.14 (2.01-2.27)
Model 1 & BMI	1 (ref.)	1.96 (1.85-2.09)
Model 1 & BMI and BMI at age 18 yrs	1 (ref.)	1.99 (1.87-2.11)
Model 1 & BMI at age 18 yrs and weight change	1 (ref.)	2.00 (1.88-2.12)
Adjustment for body fat distribution (1986-2004)[3]		
Model 1	1 (ref.)	2.18 (2.03-2.34)
Model 1 & BMI	1 (ref.)	1.99 (1.85-2.14)
Model 1 & waist and hip circumference	1 (ref.)	2.01 (1.87-2.16)
Model 1 & BMI and waist and hip circumference	1 (ref.)	1.97 (1.83-2.12)

95% CI denotes 95% confidence interval; BMI denotes body mass index; family history of diabetes denotes diabetes in one or more first-degree family members; weight change denotes weight change since age 18 yrs. All anthropometric variables were modeled as continuous variables: BMI (kg/m^2), waist circumference (cm), hip circumference (cm), weight change (kg)

[1] Restricted to participants with complete data on BMI at age 18 years (4822 diabetes events during 1,295,965 person-years of follow-up)

[2] Adjusted for age, race, socio-economic status, and lifestyle as described in the footnotes to Table 1.

[3] Restricted to participants with complete data on waist and hip circumference with follow-up starting in 1986 when data on waist and hip circumference were first collected (3201 diabetes events during 834,231 person-years of follow-up).

Body size of the parents, family history and incident diabetes

In women who had at least one parent with obesity, the baseline prevalence of overweight (BMI 25.0-29.9 kg/m^2) was 30% and the prevalence of obesity (BMI ≥ 30.0 kg/m^2) was 17% as compared with 25% and 10% respectively in women who did not have parents with obesity ($p < 0.0001$). Table 3 shows the risk of type 2 diabetes according to four categories of diabetes and obesity in the parents. Compared with women without a parental history of diabetes or obesity, the relative risk of type 2 diabetes was similar for women with a parental history of both obesity and diabetes and those with only a parental history of diabetes, but substantially weaker for women with only a parental history of obesity. The association between having only a parental history of obesity and risk of type 2 diabetes was fully explained by the higher BMI of the participants (Table 3).

Table 3. Relative risk of type 2 diabetes according to a parental history of diabetes and obesity.

Parental history of diabetes and obesity*	**DM- Obese-**	**DM- Obese+**	**DM+ Obese-**	**DM+ Obese+**
Number of cases	1620	1170	806	760
Person-years of follow-up	630,244	330,599	120,408	102,783
Adjusted relative risks (95% CI)†				
Age	1 (ref.)	1.37 (1.27-1.48)	2.61 (2.40-2.84)	2.81 (2.57-3.06)
SES/race	1 (ref.)	1.36 (1.26-1.46)	2.58 (2.37-2.81)	2.73 (2.50-2.98)
Lifestyle	1 (ref.)	1.30 (1.20-1.40)	2.43 (2.23-2.65)	2.48 (2.27-2.71)
BMI	1 (ref.)	0.98 (0.91-1.06)	2.21 (2.03-2.41)	1.77 (1.62-1.93)

DM denotes diabetes mellitus; 95% CI denotes 95% confidence interval; BMI denotes body mass index

** History of diabetes mellitus and/ or obesity in either the father or the mother.*

† Multivariate models are described in the footnotes to Table 2.

DISCUSSION

In this prospective cohort study of 73,227 women with 20 years of follow-up, we observed a direct association between a family history of diabetes and incidence of type 2 diabetes, which was similar for having a paternal or a maternal history of diabetes. A substantial part of this association could be explained by the higher BMI in persons with a family history of diabetes. Lower alcohol consumption and higher consumption of red meat and sugar-sweetened beverages modestly contributed to explaining the association between family history of diabetes and risk of type 2 diabetes.

Earlier research reported relatives risks of type 2 diabetes in individuals with self-reported parental history of diabetes ranging from 1.87 to 2.26 (1-3). These results are consistent with our findings, suggesting an approximately two-fold risk of type 2 diabetes associated with having a first-degree family member with diabetes.

In NHANES, the unadjusted odds ratio for having type 2 diabetes in the group of participants with a high familial risk compared with participants without a family history was 6.8 (18). Adjusting for sex, race, age, hypertension, household income and education had no appreciable effect on the odds ratio, but adjustment for BMI lowered the odds ratio to 5.8. We observed that generalized adiposity as reflected by BMI rather than fat distribution as reflected by waist and hip circumferences contributed to the association between family history of diabetes and diabetes risk. This agrees with studies in which having a family history of diabetes was associated with a higher BMI, but not independently with a higher waist-to-hip ratio (5-7). Furthermore, the Quebec Family Study revealed that total body fat, but not fat distribution, shared common familial determinants (19). Adoption studies have shown a strong association between the BMI of adoptees and the BMI of their biological parents (20), suggesting that the clustering of overweight in families at least partly reflects shared genetic characteristics. In addition,

variants in adiposity-related genes have been associated with a higher risk of type 2 diabetes (21). Shared genetic characteristics related to adiposity may thus contribute to a clustering of type 2 diabetes in families through increased adiposity.

In addition to adiposity, we examined the role of lifestyle factors. Consumption of red meat consumption, sugar-sweetened beverages and alcohol explained part of the association between family history of diabetes and risk of type 2 diabetes. Higher consumption of red meat and sugar-sweetened beverages and alcohol abstinence (as compared with moderate alcohol consumption) have been associated with a higher risk of type 2 diabetes (22-24). Consistent with the current finding, a parental history of diabetes was associated with lower alcohol consumption in a population-based study in the Netherlands (5). Higher consumption of red meat and sugar-sweetened beverages and alcohol abstinence (instead of moderate consumption) may thus modestly contribute to the higher risk of type 2 diabetes in persons with a family history of diabetes.

For a factor to explain a proportion of the association between a family history of diabetes and incident type 2 diabetes, it has to be both associated with risk of type 2 diabetes and shared by family members. In our study, established risk factors for diabetes such as smoking and lack of physical activity (2) did not contribute to the association between a family history and incident type 2 diabetes, suggesting that these factors did not cluster strongly within families at the age studied. This, however, does not imply that individuals with a family history of diabetes cannot benefit from adopting these lifestyle factors to lower their risk of developing type 2 diabetes. In contrast, a previous analysis of the Nurses' Health Study indicated that persons with a family history of diabetes can greatly reduce their risk of type 2 diabetes by adhering to current lifestyle guidelines on non-smoking, regular physical activity, choosing healthy sources of dietary fat and carbohydrates, and avoiding excess weight gain (25).

Our study had several strengths. The large sample size increased the precision of our estimates. Furthermore, the prospective design limited the probability of differential misclassification of risk factors and selection bias was limited due to the high response rates for the follow-up questionnaires. Our study also had several potential limitations. First, diabetes was assessed by self-report which may have led to misclassification. However, our validation study using medical records indicated that the reporting of diabetes was accurate in this medically knowledgeable population. Second, individuals with a family history of diabetes have a higher probability of being tested for diabetes as compared with the general population (26), which increases their chance of having diabetes detected once it develops. However, in a sensitivity analysis restricted to women who underwent blood glucose testing the effects of adjustment for lifestyle factors and adiposity were essentially the same as for the complete study population. Third, family history of diabetes was not specific to type 2 diabetes, which might have influenced our results. Fourth, some measurement error in the assessment of adiposity, family history, and lifestyle is likely to have occurred. We were able to use validated questionnaires and include multiple measurements of these variables in the analysis, reducing the amount of measurement error. Remaining measurement error is likely to have led to an underestimation of the proportion of the association between family history of diabetes and risk of type 2 diabetes that can be explained by adiposity and lifestyle factors. However, we cannot completely exclude the possibility that correlated error in the assessment of adiposity and lifestyle and the assessment of family history of obesity and type 2 diabetes has led to an overestimation of the explained proportions of the association between family history and risk of type 2 diabetes. Furthermore, there may be other lifestyle factors or factors that we did not measure with sufficient accuracy or in the right period of life that contribute substantially to the higher risk of type 2 diabetes associated with having a family history of diabetes. Finally, our study only included registered nurses which limited the variation in

SES and, to a lesser extent, lifestyle behaviors. In more diverse populations, SES, lifestyle factors, and adiposity may explain a greater proportion of the association between family history of diabetes and diabetes risk.

To conclude, our prospective findings confirm that having a first-degree family member with diabetes is a strong risk factor for type 2 diabetes with a similar risk associated with having a maternal and a paternal history of diabetes. A substantial part of the association between having a family history of diabetes and 20-year incidence of type 2 diabetes could be explained by excess adiposity, while dietary factors including consumption of alcohol, red meat and sugar-sweetened beverages might also play a role. Further studies on this topic with more detailed measures of family history of diabetes, adiposity, and lifestyle factors are warranted. However, the current findings in combination with recent studies of genetic risk variants (3,4) suggest that most of the association between family history of diabetes and diabetes risk remains unexplained. Further research on novel genetic and lifestyle risk factors, epigenetic risk factors, and specific gene-environment interactions is warranted to identify additional factors that mediate the strong association between having a family history of diabetes and personal risk of type 2 diabetes.

Online Appendix Table A2. Risk of type 2 diabetes according to family history of diabetes in the complete sample and only in women who underwent glucose screening (follow-up 1996-2004).*

Total sample	**No family history**	**Family history**	**Father only**	**Mother only**	**Sibling only**	**> 1 family member**
Number of cases	1870	1124	316	406	138	264
Person-years	399,989	108,869	32,898	41,597	16,794	17,580
Adjusted relative risks (95% CI)						
Age[1]	1 (ref.)	2.21 (2.05-2.38)	2.10 (1.86-2.30)	2.07 (1.86-2.31)	1.72 (1.45-2.05)	3.22 (2.82-3.66)
SES / race[2]	1 (ref.)	2.18 (2.02-2.35)	2.11 (1.87-2.38)	2.04 (1.83-2.28)	1.68 (1.41-2.00)	3.12 (2.74-3.56)
Lifestyle[3]	1 (ref.)	2.07 (1.92-2.24)	2.00 (1.77-2.26)	1.95 (1.75-2.18)	1.63 (1.37-2.95)	2.88 (2.53-3.29)
BMI[4]	1 (ref.)	1.88 (1.74-2.03)	1.85 (1.64-2.09)	1.78 (1.59-1.99)	1.47 (1.23-1.75)	2.52 (2.21-2.88)
Women with screening only	**No family history**	**Family history**	**Father only**	**Mother only**	**Sibling only**	**> 1 family member**
Number of cases	1568	993	278	364	124	227
Person-years	218,005	70,030	20,755	26,742	10,632	11,901
Adjusted relative risks (95% CI)*						
Age[1]	1 (ref.)	1.97 (1.82-2.13)	1.89 (1.66-2.15)	1.88 (1.68-2.12)	1.58 (1.31-1.90)	2.66 (2.31-3.06)
SES / race[2]	1 (ref.)	1.98 (1.82-2.15)	1.93 (1.69-2.20)	1.89 (1.68-2.12)	1.57 (1.30-1.90)	2.64 (2.29-3.04)
Lifestyle[3]	1 (ref.)	1.89 (1.74-2.05)	1.82 (1.60-2.08)	1.81 (1.61-2.04)	1.53 (1.27-1.84)	2.47 (2.14-2.85)
BMI[4]	1 (ref.)	1.73 (1.59-1.87)	1.68 (1.48-1.92)	1.68 (1.49-1.88)	1.39 (1.15-1.68)	2.19 (1.90-2.53)

95% CI denotes 95% confidence interval; BMI denotes body mass index; family history of diabetes denotes diabetes in one or more first-degree family members.

** Since 1998, women were asked biennially to report whether they had been screened for fasting blood glucose in the previous two years. Therefore, the multivariate Cox regression was repeated for the follow-up cycles from 1996 to 2004 separately for 1). The entire study population; and 2). Only women who reported to have been tested for fasting blood glucose during a 2-year follow-up period (e.g. women who reported that they did not have a glucose test between 2000 and 2002 were excluded for the analysis in that period).*

[1] Adjusted for age (continuous in months)

[2] Model 1 additionally adjusted for occupation father (none, professional/managerial, clerical/sales/services), occupation mother (none; professional/managerial; clerical/sales/services), husband's highest degree (< high school, some HS, HS gad, college grad, grad school), participants highest degree (registered nurse, bachelor, master, doctoral), race (white, black, Asian, other)

[3] Model 2 additionally adjusted for smoking (never, past, current smokers: ≤ 14, 15-24, ≥ 25 cigs/day), physical activity (< 1.0, 1.0-1.9, 2.0-3.9, 4.0-6.9, ≥ 7.0 hours/week), intake of coffee (0, 0.1-0.9, 1.0-1.9, 2.0-3.9, 4.0-5.9, ≥ 6 cups/day), alcohol (0, 0.1-4.9, 5.0-9.9, ≥ 10.0 g/day), fruit (quintiles), vegetables (quintiles), sugar-sweetened beverages (quintiles), whole grain (quintiles) , red meat (quintiles), trans-fat (quintiles), total energy (quintiles), and polyunsatured-to-saturated fat ratio (quintiles)

[4] Model 3 additionally adjusted for BMI (<21, 21-23, 23-25,25-27,27-30,30-33,33-35,35-40,>40 kg/m^2)

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