

# 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

ESTHER VAN 'T RIET, MSc<sup>1,2,3</sup>  
 JACQUELINE M. DEKKER, PhD<sup>2,3</sup>  
 QI SUN, PhD<sup>1</sup>

GIEL NIJPELS, MD, PHD<sup>2,4</sup>  
 FRANK B. HU, MD, PHD<sup>1,5,6</sup>  
 ROB M. VAN DAM, PHD<sup>1,5,6</sup>

**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 BMI was calculated. The relative risk of type 2 diabetes was estimated using Cox proportional hazards analysis.

**RESULTS** — We documented 5,101 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) compared with the risk in 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% (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% (0.8–1.3), 4.8% (4.3–5.3), and 2.8% (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.

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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).

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 adiposity was observed in individuals 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 be-

tween family history of diabetes and risk of type 2 diabetes has not been examined in prospective studies. Therefore, we prospectively evaluated the following hypotheses in the Nurses' Health Study (NHS): 1) a large proportion of the association between family history of diabetes and risk of type 2 diabetes can be explained by greater adiposity and 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.

## RESEARCH DESIGN AND METHODS

The 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 ~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 nonmelanoma skin cancer) or cardiovascular diseases at baseline ( $n = 4,934$ ), because the diagnosis of these diseases could have interfered with self-reports of lifestyle and family history. Women with incident types of diabetes other than type 2 diabetes or unconfirmed type 2 diabetes were also excluded ( $n = 1,480$ ). Moreover, women with missing information for diabetes status, family history of diabetes, date of birth, weight, or height were excluded ( $n = 1,787$ ). As a result, 73,227 women remained for the present analysis.

From the <sup>1</sup>Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the <sup>2</sup>EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands; the <sup>3</sup>Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands; the <sup>4</sup>Department of General Practice, VU University Medical Center, Amsterdam, the Netherlands; the <sup>5</sup>Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and the <sup>6</sup>Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Corresponding author: Esther van 't Riet, e.vanriet@vumc.nl.

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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 age (50.6 and 50.2 years), the proportion of participants with obesity (13.3 and 12.3%), mean weight change since age 18 years (28.3 and 27.6 kg), and the proportion of participants reporting to drink no alcohol (31.5 and 30.6%) or  $>10$  g of alcohol/day (23.6 and 24.0%).

### **Assessment of family history of diabetes and parental body size**

Women were asked to report whether 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 1 (very lean) to 9 (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 nonobese (image 1–5) or obese (image 6–9).

### **Assessment of lifestyle, socioeconomic status, race, and adiposity**

Dietary information was collected using a semiquantitative FFQ included in the questionnaires mailed to the participants every 2–4 years. 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 2–4 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 her husband, father's and moth-

er's occupation, and race was assessed in the 1992 questionnaire.

Height was assessed in the baseline questionnaire and body weight every 2 years. BMI was calculated as weight in kilograms divided by the square of height in meters. 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 and hip circumferences were 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 NHS aged 41–65 years. Pearson correlations between self-reported and technician-measured weight, waist circumference, and hip circumference were high ( $r = 0.97, 0.89, \text{ and } 0.84$ , respectively) (12).

### **Ascertainment of type 2 diabetes**

Women who reported having diabetes in the biennial questionnaires were mailed a supplemental questionnaire to gather 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  $\geq 7.8$  mmol/L, random plasma glucose of  $\geq 11.1$  mmol/L, or plasma glucose  $\geq 11.1$  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 cutoff point for fasting plasma glucose concentrations to 7.0 mmol/L. In a subsample, type 2 diabetes that was confirmed by the supplementary questionnaire was consistent with medical record reviews by an endocrinologist in 98% of the women (15).

### **Statistical analysis**

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 hazards analysis was used to estimate the relative risk (RR) for type 2 diabetes according to family history. To evaluate the contribution of different covariates on the association between family history and di-

abetes risk, we used multivariate models with the following adjustments: 1) age; 2) age, socioeconomic status (SES) (occupation of the father, occupation of the mother, husband's highest degree, and participant's highest degree), and race; 3) age, SES, race, and lifestyle (smoking, physical activity, polyunsaturated/saturated fat intake ratio and intakes of coffee, alcohol, fruit, vegetables, sugar-sweetened beverages, whole grains, red meat, trans-fat, and total energy); and 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 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 2 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 dietary variables we used cumulative updating to reduce within-person variation (16). The proportion of the association explained by including different covariates in the model was calculated based on the change in regression coefficients, using the method of Lin et al. (17) to calculate the 95% CI.

All  $P$  values were two-tailed, and  $P < 0.05$  was considered to be statistically significant. Inclusion of multiplicative interaction terms between time and family history in the multivariate models suggested that the proportional hazards assumption was not violated. The SAS statistical program (version 9.1; SAS Institute, Cary, NC) was used for all analyses.

**RESULTS**— We documented 5,101 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**

We evaluated baseline characteristics according to family history of diabetes. Compared with participants without a family history, participants with a family history were slightly older, had a higher

Table 1—RR of type 2 diabetes according to family history of diabetes during the 20-year follow-up (1984–2004)

	No family history	Family history	Father only	Mother only	Sibling only	>1 family member
n	3,132	1,969	517	727	240	485
Person-years	1,075,728	289,889	90,785	111,880	42,423	44,800
Adjusted RRs (95% CI)						
Age*	1 (referent)	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†	1 (referent)	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‡	1 (referent)	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§	1 (referent)	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)

A family history of diabetes denotes diabetes in  $\geq 1$  first-degree family members. \*Adjusted for age (continuous in months). †Model 1 additionally adjusted for occupation of the father (none, professional/managerial, or clerical/sales/services), occupation of the mother (none, professional/managerial, or clerical/sales/services), husband's highest degree (less than high school, some high school, high school graduate, college graduate, or graduate school), participant's highest degree (registered nurse, bachelor, master, or doctoral), and race (white, black, Asian, or other). ‡Model 2 additionally adjusted for smoking (never, past, or current smoker:  $\leq 14$ , 15–24, or  $\geq 25$  cigarettes/day), physical activity ( $< 1.0$ , 1.0–1.9, 2.0–3.9, 4.0–6.9, or  $\geq 7.0$  h/week), intake of coffee (0, 0.1–0.9, 1.0–1.9, 2.0–3.9, 4.0–5.9, or  $\geq 6$  cups/day), alcohol (0, 0.1–4.9, 5.0–9.9, or  $\geq 10.0$  g/day), fruit (quintiles), vegetables (quintiles), sugar-sweetened beverages (quintiles), whole grains (quintiles), red meat (quintiles), trans-fat (quintiles), total energy (quintiles), and polyunsaturated-to-saturated fat ratio (quintiles). §Model 3 additionally adjusted for BMI ( $< 21$ , 21–23, 23–25, 25–27, 27–30, 30–33, 33–35, 35–40, or  $> 40$  kg/m<sup>2</sup>).

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 (supplementary Table A1, available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc09-1586/DC1>).

### 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 adjustment for age, the RR of type 2 diabetes in participants with a family history was 2.27 (95% CI 2.14–2.40) compared with that of participants without a family history. The RR 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 socioeconomic 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 finding, we included all factors separately in the model. Consumption of alcohol, red meat, and sugar-sweetened beverages explained 4.8% (95% CI 4.3–5.3), 1.1% (0.8–1.3), and 2.8% (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 dia-

betes and risk of type 2 diabetes (Table 1), explaining 21.1% (19.4–22.9) of the association.

We conducted a sensitivity analysis restricted to women who underwent blood glucose screening for the 1996–2004 period in which this information was available. Among the screened women, the effect of additionally adjusting for SES and race, lifestyle, and adiposity was essentially the same as that for the complete study population (supplementary Table A2, available in an online appendix).

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 consideration of measures of body fat distribution nor adolescent BMI explained a substantially greater proportion of the association between family history and diabetes risk compared with the model that only included BMI.

### 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<sup>2</sup>) was 30% and the prevalence of obesity (BMI  $\geq 30.0$  kg/m<sup>2</sup>) was 17% compared with

Table 2—RR 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)*		
Model 1†	1 (referent)	2.14 (2.01–2.27)
Model 1 and BMI	1 (referent)	1.96 (1.85–2.09)
Model 1 and BMI and BMI at age 18 years	1 (referent)	1.99 (1.87–2.11)
Model 1 and BMI at age 18 years and weight change	1 (referent)	2.00 (1.88–2.12)
Adjustment for body fat distribution (1986–2004)‡		
Model 1	1 (referent)	2.18 (2.03–2.34)
Model 1 and BMI	1 (referent)	1.99 (1.85–2.14)
Model 1 and waist and hip circumference	1 (referent)	2.01 (1.87–2.16)
Model 1 and BMI and waist and hip circumference	1 (referent)	1.97 (1.83–2.12)

Family history of diabetes denotes diabetes in  $\geq 1$  first-degree family members. Weight change denotes weight change since age 18 years. All anthropometric variables were modeled as continuous variables: BMI (weight in kilograms divided by the square of height in meters), waist circumference (centimeters), hip circumference (centimeters), and weight change (kilograms). \*Restricted to participants with complete data on BMI at age 18 years (4,822 diabetes events during 1,295,965 person-years of follow-up). †Adjusted for age, race, SES, and lifestyle as described in the footnotes to Table 1. ‡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 (3,201 diabetes events during 834,231 person-years of follow-up).

Table 3—RR of type 2 diabetes according to a parental history of diabetes and obesity

Parental history of diabetes and obesity*	Diabetes <sup>-</sup>	Diabetes <sup>-</sup>	Diabetes <sup>+</sup>	Diabetes <sup>+</sup>
	Obese <sup>-</sup>	Obese <sup>+</sup>	Obese <sup>-</sup>	Obese <sup>+</sup>
n	1,620	1,170	806	760
Person-years of follow-up	630,244	330,599	120,408	102,783
Adjusted RRs (95% CI)†				
Age	1 (referent)	1.37 (1.27–1.48)	2.61 (2.40–2.84)	2.81 (2.57–3.06)
SES/race	1 (referent)	1.36 (1.26–1.46)	2.58 (2.37–2.81)	2.73 (2.50–2.98)
Lifestyle	1 (referent)	1.30 (1.20–1.40)	2.43 (2.23–2.65)	2.48 (2.27–2.71)
BMI	1 (referent)	0.98 (0.91–1.06)	2.21 (2.03–2.41)	1.77 (1.62–1.93)

\*History of diabetes and/or obesity in either the father or the mother. †Multivariate models are described in the footnotes to Table 1.

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 that for women without a parental history of diabetes or obesity, the RR 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).

**CONCLUSIONS**— 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 individuals 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.

Consistent with our findings, earlier research reported RRs of type 2 diabetes in individuals with self-reported parental history of diabetes ranging from 1.87 to 2.26 (1–3). In the National Health and Nutrition Examination Survey, adjustment for sex, race, age, hypertension, household income, and education had no

appreciable effect on the association between family history of diabetes and prevalence of type 2 diabetes, but adjustment for BMI did weaken the association (18). In our study, generalized adiposity as reflected by BMI rather than circumference measures of fat distribution contributed to the association between family history of diabetes and diabetes risk. This finding 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).

In addition to adiposity, we examined the role of lifestyle factors. Consumption of red meat, 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 (compared with moderate alcohol consumption) have been associated with a higher risk of type 2 diabetes (20–22). 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 individuals 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 finding, 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 (23).

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 because of 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 compared with the general population (24), 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 those 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. This has probably 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 diabetes has led to an overestimation of the explained proportions of the association between family history and risk of type 2 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 summarize, 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, whereas 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, lifestyle in other periods of life, 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.

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