Parental History of Diabetes Modifies the Association Between Abdominal Adiposity and Hyperglycemia

ROB M. VAN DAM, MSC[1]
JOLANDA M.A. BOER, PHD[1]
EDITH J.M. FESKENS, PHD[1]
JAAP C. SEIDELL, PHD[1,2]

OBJECTIVE — To examine whether the association between abdominal obesity and hyperglycemia differs according to the presence of a parental history of diabetes.

RESEARCH DESIGN AND METHODS — We conducted a cross-sectional study of 3,068 men and women, aged 20–65 years, without known diabetes who were fasting participants of a population-based study in three Dutch towns. Hyperglycemia was defined as a fasting plasma glucose concentration of 6.1 mmol/l (American Diabetes Association criterion). Waist circumference was categorized according to previously defined waist action levels. All estimates were adjusted for age and town.

RESULTS — The regression coefficients for the association between waist circumference and fasting plasma glucose were larger in participants who had a parental history of diabetes than in those who did not (men $\beta = 0.31$ vs. 0.16 mmol/SD, P [for interaction] = 0.003; women $\beta =$ 0.24 vs. 0.11 mmol/SD, $P = 0.002$). Furthermore, larger waist circumference (men ≥94 vs. <94 cm, women ≥88 vs. <80 cm) was associated with a greater excess prevalence of hyperglycemia in participants who had a parental history of diabetes than in those who did not (men 12.4 vs. 2.0%, $P = 0.03$; women 13.6 vs. 5.9%, $P = 0.05$). Adjustment for physical activity, alcohol intake, smoking, and educational level did not materially change the results.

CONCLUSIONS — These findings indicate that the association between abdominal obesity and hyperglycemia is stronger in the presence of a parental history of diabetes. Blood glucose screening may be warranted at lower levels of waist circumference in individuals with a parental history of diabetes.

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Obesity and family history of diabetes are major predictors of type 2 diabetes (1–4). Both factors are relatively easy to assess and are widely used for the identification of individuals with undiagnosed diabetes (5,6). Obesity affects hyperglycemia through a decrease in insulin sensitivity. Abdominal obesity seems to have a particularly strong association with insulin resistance (7) and risk of type 2 diabetes (3,4). A parental history of diabetes is believed to reflect genetic susceptibility to hyperglycemia (8). Presence of a parental history is associated with impairments in insulin sensitivity and/or insulin secretion (1,9) and may therefore modify the effect of obesity on glucose homeostasis. If the association between obesity and hyperglycemia is different in individuals with a parental history of diabetes, this may affect decisions about weight reduction and screening for diabetes.

Although both obesity and parental history of diabetes have been studied extensively, information on the effect of combinations of these risk factors on hyperglycemia is limited (1,2,10–13). Most studies were either too small to provide precise estimates (1,12) or studied only diagnosed diabetes (10,13). Studies of diagnosed diabetes may be affected by detection bias because individuals with obesity or a family history of diabetes are more likely to be tested for diabetes, especially if both risk factors are present.

We examined whether the association between obesity and hyperglycemia differed according to presence of a parental history of diabetes in 3,068 men and women, aged 20–65 years, without known diabetes. We focused on waist circumference because this measure reflects both abdominal and general obesity and is practical for use in health promotion (14).

RESEARCH DESIGN AND METHODS

Study population

The monitoring of risk factors and health in the Netherlands (MORGEN study) was a cross-sectional study of men and women, aged 20–65 years, who were examined between 1993 and 1997 (14). Participants were from a random sample (stratified by sex and 5-year age groups) from the civil registries of the towns Amsterdam, Maastricht, and Doetinchem. Of the 22,766 participants (45% response), 3,580 were fasting at the time of the physical examination (reported to have not eaten anything after midnight).

Individuals who were pregnant (n = 16) or had known diabetes (n = 30) were excluded from the study. In addition, we excluded individuals with missing values for plasma glucose concentration (n = 129), anthropometric measures (n = 8), potential confounders (n = 57), or parental history of diabetes (n = 12) as well as those who reported that they did not know whether their parents had diabetes (n = 286). A total of 3,068 individuals remained for the analyses.

From the [1]Department of Chronic Diseases Epidemiology, National Institute of Public Health and the Environment, Bilthoven; and the [2]Institute for Research in Extramural Medicine, Free University Amsterdam, The Netherlands.

Address correspondence to Rob M. van Dam, Department of Chronic Diseases Epidemiology, National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands. E-mail: rob.van.dam@rivm.nl.

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Abbreviations: WHO, World Health Organization; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of the study population by parental history of diabetes (the MORGEN study 1993–1997)*

	Men			Women		
	Parental history		95% CI of difference	Parental history		95% CI of difference
	Yes (n = 250)	No (n = 1,384)		Yes (n = 256)	No (n = 1,178)	
Age (years)	43.4	39.6	2.3 to 5.2	41.4	37.9	2.0 to 4.9
Current cigarette smokers (%)	46.9	48.8	−8.8 to 4.9	52.8	50.8	−4.8 to 8.8
Alcohol intake						
Abstainers (%)	30.8	23.6	1.3 to 13.1	58.6	50.7	1.2 to 14.7
≥1 drink/day (%)	55.6	63.4	−14.3 to −1.2	22.0	28.2	−12.2 to 0.2
Physical activity* ≥3.5 h/week (%)	40.6	43.3	−9.4 to 4.0	40.3	43.4	−9.8 to 3.5
Low educational level† (%)	51.8	46.5	−1.3 to 11.9	57.4	50.0	1.0 to 13.7
Obesity						
Waist circumference (cm)	94.2	91.9	0.9 to 3.6	82.5	80.2	0.8 to 3.7
Waist action level 1 to 2‡ (%)	26.4	21.7	−0.9 to 10.3	20.8	22.7	−7.6 to 3.7
Waist action level ≥2§ (%)	26.0	18.4	2.4 to 12.8	28.9	21.3	2.2 to 13.1
WHR	0.919	0.906	0.004 to 0.02	0.794	0.785	0.001 to 0.02
WHR, BMI-adjusted	0.908	0.906	−0.01 to 0.01	0.791	0.789	−0.01 to 0.01
BMI (kg/m^2)	26.4	25.4	0.5 to 1.5	25.8	24.6	0.5 to 1.7
Hyperglycemia						
Prevalence of hyperglycemia‖ (%)	22.2	12.6	5.0 to 14.3	11.1	5.8	2.0 to 8.7
Plasma glucose (mmol/l)	5.7	5.3	0.2 to 0.5	5.2	5.0	0.1 to 0.3

Data are means unless otherwise indicated. *Adjusted for age (years) and town of examination (Amsterdam, Doetinchem, Maastricht) (except for age); differences are statistically significant ($P < 0.05$) if the 95% CI does not include 0. *Nonoccupational physical activity of at least moderate intensity; †junior secondary school or less; ‡94.0–101.9 cm for men and 80.0–87.9 cm for women, §≥102.0 cm for men and ≥88.0 cm for women; ‖plasma glucose concentration ≥6.1 mmol/l.

Examinations

Anthropometric measurements were made according to World Health Organization (WHO) recommendations (15) by trained paramedic staff with participants in standing position, wearing only light indoor clothing and no shoes. Body weight was measured to the nearest 100 g using calibrated scales, height was measured to the nearest 0.5 cm, waist circumference was measured in duplicate at the level midway between the lowest rib margin and iliac crest to the nearest 0.5 cm, and hip circumference was measured in duplicate at the widest trochanters to the nearest 0.5 cm. We used the mean of the duplicate measurements and calculated the BMI (weight divided by the square of height) and the ratio of the waist and hip circumference. Waist circumference was categorized using the waist action levels proposed by Lean et al. (14) as cutoff points for men (action level 1 = 94.0 cm, action level 2 = 102 cm) and for women (action level 1 = 80.0 cm, action level 2 = 88.0 cm).

We used a self-administered questionnaire to assess cigarette smoking, nonoccupational physical activity of at least moderate intensity, consumption of alcoholic beverages, educational level, presence of known diabetes, and parental history of diabetes. The questionnaires were checked by paramedic staff, and questions were repeated if answers were missing or incorrect.

Venous blood samples for glucose determination were collected in tubes with sodium fluoride. Plasma glucose concentrations were measured using the hexokinase method by a WHO standardized laboratory at the Academic Dijkzigt Hospital of the Erasmus University in Rotterdam The Netherlands. The coefficient of variation was 1.0% within runs and 1.4% between runs. Hyperglycemia was defined as impaired fasting glucose or diabetes according to the WHO criteria (16) and the American Diabetes Association (5) (i.e., plasma glucose concentrations ≥ 6.1 mmol/l). We included impaired fasting glucose to identify individuals in our relatively young population who were likely to develop diabetes.

Statistics

We used the General Linear Models procedure of the SAS software (SAS Institute, Cary, NC) (17) to calculate adjusted means, prevalence, 95% CIs, and P values for interaction. Tests for statistical interaction were conducted by including cross-product terms of parental history and measures of obesity in an additive regression model. Estimates were adjusted for age (years) and town of examination (Amsterdam, Doetinchem, Maastricht). We also calculated estimates with additional adjustment for smoking (ex, current, never), nonoccupational physical activity of at least moderate intensity (h/week), alcohol intake (abstainer or 0.1–0.9, 1.0–2.9, or ≥3 drinks/day), and educational level (junior secondary school or less, secondary school, vocational college or university). Before waist-to-hip ratio (WHR) or hip circumference was included with BMI in a multivariate model, these measures were adjusted for BMI using the residual method (18) to avoid potential problems with collinearity. All analyses were conducted for men and women separately. All P values were two-sided.

RESULTS — A parental history of diabetes was reported by 15.3% of the men and 17.9% of the women. Participants with a parental history of diabetes were older, had a lower alcohol intake, and were more likely to have a lower educational level than the other participants (Table 1). Furthermore, parental history of diabetes was associated with higher body fatness as measured by waist circumference, WHR, and BMI. After adjust-

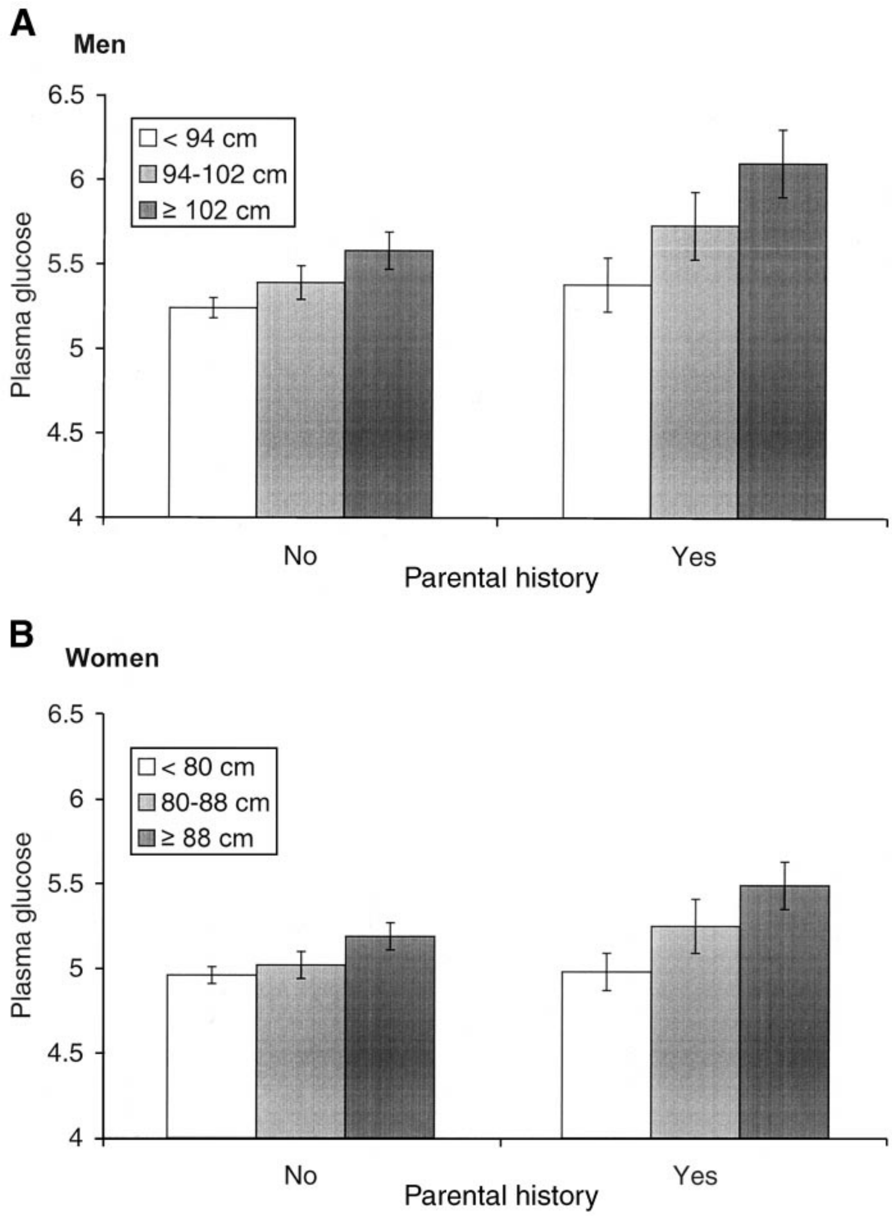

Figure 1—*Fasting plasma glucose concentration by waist action levels and parental history of diabetes in men and women. Mean waist circumference measurements were 84, 98, and 108 cm for men with a parental history of diabetes; 85, 98, and 108 cm for men without a parental history of diabetes; 72, 83, and 97 cm for women with a parental history of diabetes; and 73, 83, and 99 cm for women without a parental history of diabetes.*

ment for BMI, the WHR was no longer associated with parental history of diabetes. Presence of a parental history of diabetes was also associated with higher plasma glucose concentrations and higher prevalence of hyperglycemia.

The association between categories of waist circumference and fasting plasma glucose concentrations, stratified by parental history of diabetes, is shown in Fig. 1. The positive association between waist circumference and fasting plasma glucose concentrations was stronger in individuals who had a parental history of diabetes than in those who did not (Fig. 1 and Table 2).

To examine whether the interaction with parental history in relation to fasting plasma glucose was specific for waist circumference, we also obtained results for BMI and WHR. Both BMI and WHR were highly correlated with waist circumference (Pearson correlations: men, 0.86 for waist and BMI, 0.84 for waist and WHR; women, 0.86 for waist and BMI, 0.78 for waist and WHR). A similar interaction with parental history of diabetes was observed for waist, WHR, and BMI among women; among men, the association between BMI and fasting plasma glucose did not significantly differ by parental history of diabetes (Table 2). The results remained essentially the same after adjustment for physical activity, alcohol intake, cigarette smoking, and educational level. After adjustment for BMI, WHR remained strongly associated with plasma glucose in participants with a parental history of diabetes but not in the other participants (Table 2). In women with a parental history of diabetes, BMI-adjusted hip circumference was inversely associated with plasma glucose (β −0.12 [SE 0.05] mmol/l per SD); this association was weaker in women who did not have a parental history of diabetes (β −0.03 [SE 0.02] mmol/l per SD; *P* [for interaction] = 0.05). Therefore, both waist and hip circumference contributed to the interaction between parental history and WHR in women. In men, no associations between BMI-adjusted hip circumference and plasma glucose were observed.

We also examined combinations of waist circumference and parental history of diabetes in relation to prevalence of hyperglycemia. Among men with a parental history of diabetes, a waist circumference higher than action level 1, relative to lower than action level 1, was associated with greater excess prevalence of hyperglycemia in individuals who had a parental history of diabetes (12.4%; 95% CI 3.8–21.0) than in those who did not (2.0%; −1.9 to 5.8; *P* [for interaction] = 0.03). Specifically, a waist circumference between action levels 1 and 2 was associated with a substantial excess prevalence of hyperglycemia in men who had a parental history of diabetes but not in other men (Table 3). Among women, a waist circumference above action level 2, relative to below action level 1, was associated with a larger excess prevalence in hyperglycemia in individuals who had a parental history of diabetes (13.6%, 6.6–20.6) than in those who did not (5.9%, 2.1–9.7) (Table 3).

CONCLUSIONS— In this cross-sectional study of 3,068 men and women aged 20–65 years, the association between obesity and fasting plasma glucose was stronger in individuals with a paren-

Table 2—*Regression coefficients for the association between measures of obesity and plasma glucose concentrations (mmol/l) by parental history of diabetes (the MORGEN study 1993–1997)*

Measure and adjustments	Men			Women		
	Parental history			Parental history		
	Yes (n = 250)	No (n = 1,384)	P for interaction	Yes (n = 256)	No (n = 1,178)	P for interaction
Waist circumference						
Age and town*	0.31 (0.09)	0.16 (0.02)	0.003	0.24 (0.05)	0.11 (0.02)	0.002
Multivariate†	0.28 (0.09)	0.16 (0.02)	0.003	0.24 (0.05)	0.11 (0.02)	0.003
WHR						
Age and town*	0.35 (0.10)	0.13 (0.02)	<0.0001	0.28 (0.05)	0.08 (0.02)	<0.0001
Multivariate†	0.31 (0.10)	0.13 (0.02)	<0.0001	0.28 (0.05)	0.08 (0.02)	<0.0001
BMI‡	0.23 (0.09)	0.03 (0.02)	<0.0001	0.18 (0.06)	0.02 (0.02)	0.006
BMI						
Age and town*	0.21 (0.08)	0.16 (0.02)	0.06	0.22 (0.04)	0.12 (0.02)	0.006
Multivariate†	0.18 (0.09)	0.15 (0.02)	0.21	0.22 (0.05)	0.12 (0.02)	0.009

Data are regression coefficients (SE) for 1-SD difference in measure of obesity in men (waist 11.1 cm, WHR 0.074, BMI-adjusted WHR 0.058, BMI 3.7 kg/m^2) and women (waist 11.6 cm, WHR 0.071, BMI-adjusted WHR 0.062, BMI 4.7 kg/m^2). *Adjusted for age (years) and town of examination (Amsterdam, Doetinchem, Maastricht);†multivariate denotes additional adjustment for nonoccupational physical activity of at least moderate intensity (h/week), alcohol intake (abstainer, 0.1–0.9, 1.0–2.9, ≥3 drinks/day), smoking (ex, current, never), and educational level (junior secondary school or less, secondary school, or vocational college or university); ‡multivariate model with additional adjustment for BMI (kg/m^2).

tal history of diabetes than in those without such a history. This difference in association was more pronounced for measures of abdominal obesity (waist circumference and WHR) than for BMI, which reflects general adiposity. In addition, higher categories of waist circumference (at or above action level 1 for men, at or above action level 2 for women) were associated with larger excess in the prevalence of hyperglycemia in the presence of a parental history of diabetes.

Strengths of our study included the large number of participants, the ability to consider potential confounding by lifestyle factors, the examination of different measures of obesity, and the use of plasma glucose concentrations as an end point. Cross-sectional studies of diagnosed diabetes are prone to recall bias because a diagnosis of diabetes may increase awareness of the presence of diabetes in family members. In addition, studies of diagnosed diabetes may be affected by detection bias because individuals with obesity or a family history of diabetes are more likely to be tested for diabetes. In the present study, the possibility of recall and detection bias was minimized by the exclusion of individuals with known diabetes.

A potential limitation of our study was that the individuals included in the analyses were not identical to the source population because of nonresponse in the MORGEN study and restriction to individuals who reported to have fasted during blood collection. However, to cause selection bias, participation must be associated with both exposure (i.e., parental history, waist circumference) and end point (hyperglycemia). Selective participation with regard to hyperglycemia seems unlikely because plasma glucose concentrations were unknown to the participants. Furthermore, the fasting subgroup differed from the total MORGEN sample in some respects (e.g., more likely to be smokers and to be living in a large

Table 3—*Prevalence (%) of hyperglycemia by parental history of diabetes and action levels of waist circumference (the MORGEN study 1993–1997)*

	Men			Women		
	Parental history		P for interaction	Parental history		P for interaction
	Yes	No		Yes	No	
Prevalence						
Waist action level<1*	15.2 (15/105)	11.7 (84/842)	—	8.4 (8/120)	4.4 (22/668)	—
Waist action levels 1–2†	27.7 (22/71)	11.4 (38/296)	—	9.6 (6/56)	5.1 (15/265)	—
Waist action level ≥2‡	27.8 (23/74)	16.7 (48/246)	—	20.0 (18/80)	10.3 (28/245)	—
Difference with lowest waist category						
Waist action levels 1–2†	12.4 (2.2 to 22.7)	−0.3 (−4.9 to 4.3)	0.02	3.2 (−4.5 to 11.0)	0.7 (−2.9 to 4.2)	0.55
Waist action level ≥2‡	12.6 (2.5 to 22.7)	5.0 (0.1 to 10.0)	0.18	13.6 (6.6 to 20.6)	5.9 (2.1 to 9.7)	0.05

Data are % (*n/N*) and % (95% CI). Hyperglycemia indicates fasting plasma glucose ≥6.1 mmol/l; percentages are adjusted for age (years) and town of examination (Amsterdam, Doetinchem, Maastricht). *<94.0 cm for men and <80.0 cm for women; †94.0–101.9 cm for men and 80.0–87.9 cm for women; ‡≥102.0 cm for men and ≥88.0 cm for women.

city), but obesity and parental history of diabetes were similar in the fasting subgroup and the total study population (waist circumference higher than action level 2 was 20 vs. 18% in men, 23 vs. 25% in women; parental history of diabetes was 15.4 vs. 15.5% in men, 17.4 vs. 17.6% in women [age- and town-adjusted percentages]).

Although assessment of fasting status by self-report may have resulted in some misclassification, this could only have contributed to the observed interaction in the unlikely event that this misclassification was associated with both adiposity and parental history of diabetes. Another potential source of misclassification was the possibility that reported presence of a parental history of diabetes included cases of parental type 1 diabetes. Of the participants with a parental history of diabetes, only 4% ($n = 20$) had a parent with a diagnosis of diabetes before 35 years of age; exclusion of these participants did not appreciably change the results.

Consistent with our findings, in a cross-sectional study of female members of a weight-control club, obesity was associated with a greater excess prevalence of diagnosed diabetes in individuals who had a family history of diabetes than in those who did not (10). In a prospective study, the odds ratio for the association between BMI and diabetes was similar in individuals with and without a diabetic sibling (2). Because the risk for diabetes was higher in participants with a diabetic sibling, the similarity of the odds ratios implies that BMI was associated with larger absolute differences in diabetes risk in those with a diabetic sibling. Such a statistical interaction on an additive scale suggests some sort of biological interaction and is most relevant for public health because it provides information on excess disease prevalence and its related health burden (19). In a study of elderly Finnish individuals, a high BMI or WHR was associated with a greater excess prevalence of glucose intolerance in men with a family history of diabetes relative to the other men (11). However, this was not observed in the female participants, and no significant interaction between BMI or WHR and family history of diabetes in relation to 2-h glucose concentrations was observed (11). These results were partly inconsistent with our findings, possibly due to the age difference between the study populations because the association between anthropometric measures and obesity changes with aging (20).

In the present study, a parental history of diabetes was associated with a higher BMI but not with a higher BMI-adjusted WHR. This agrees with earlier studies that also observed a stronger association with BMI than with WHR (9,21), suggesting that a parental history of diabetes is associated with general obesity rather than abdominal fat distribution. Therefore, our study suggests that individuals with a parental history of diabetes have both higher obesity and a greater susceptibility to the adverse effects of obesity on glycemia.

In numerous studies, having a first-degree relative with diabetes was associated with impairments in insulin secretion and/or insulin sensitivity (1,8,9). These observations may provide mechanistic explanations for our finding that a parental history of diabetes modifies the effect of obesity on hyperglycemia. For example, impairment in insulin secretion may reduce the ability of individuals with a parental history of diabetes to compensate adequately for the detrimental effect of body fat on insulin sensitivity. Also, reduced insulin-mediated suppression of lipolysis in adipose tissue has been observed in individuals with first-degree relatives with type 2 diabetes (22), which may aggravate the excess release of free fatty acids in the presence of a higher degree of obesity. Reduced suppression of lipolysis would be especially detrimental in combination with high intra-abdominal obesity (or anthropometric surrogates such as waist circumference) because this fat deposition already has a low responsiveness to the antilipolytic effect of insulin (23). Prospective studies with estimates of insulin secretion and insulin sensitivity are required to elucidate the mechanistic background of our results.

Our results indicate that in individuals with a parental history of diabetes, especially men, waist circumference may identify hyperglycemia better than BMI. In individuals without a parental history of diabetes, waist circumference and BMI were similarly associated with fasting plasma glucose. Waist circumference reflects both abdominal and general obesity (24) and correlates well with the amount of intra-abdominal fat (23). Previous studies showed that waist circumference is also strongly associated with hypertension (24), dyslipidemia (24), insulin resistance (7), and the risk of clinical diabetes (3,4), cardiovascular diseases (4), cancer (4), and premature mortality (25). Because waist circumference requires only a single measurement and no calculations, it seems to be practical for self-assessment of obesity and use in health promotion to increase awareness of the need for weight management (14). WHR requires an additional measurement, and the hip component complicates its interpretation. In our analysis, a smaller hip circumference than expected from BMI was associated with a higher fasting glucose concentration among women with a parental history of diabetes. This association has been observed previously and may reflect an association between peripheral muscle atrophy and hyperglycemia (26).

In conclusion, we observed a stronger association between abdominal obesity and hyperglycemia in individuals who had a parental history of diabetes than in those who did not. Our results underscore the importance of considering both family history of diabetes and degree of adiposity when deciding whether to screen for diabetes. Blood glucose screening may be warranted at a lower level of waist circumference in individuals who have a parental history of diabetes compared with those who do not.

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