Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study[1–3]

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ABSTRACT

Background: The higher risk of type 2 diabetes in persons with a high waist-to-hip ratio (WHR) or waist-to-thigh ratio (WTR) has mostly been attributed to increased visceral fat accumulation. However, smaller hip or thigh circumference may also explain the predictive value of the WHR or WTR for type 2 diabetes.

Objective: This study considered prospectively the association of hip and thigh circumferences, independent of waist circumference, with the incidence of type 2 diabetes.

Design: The Hoorn Study is a population-based cohort study of diabetes. A total of 1357 men and women aged 50–75 y and non-diabetic at baseline participated in the 6-y follow-up examination. Glucose tolerance was assessed by use of a 75-g oral-glucose-tolerance test. Baseline anthropometric measurements included body mass index (BMI) and waist, hip, and thigh circumferences.

Results: Logistic regression analyses showed that a 1-SD larger hip circumference gave an odds ratio (OR) for developing diabetes of 0.55 (95% CI: 0.36, 0.85) in men and 0.63 (0.42, 0.94) in women, after adjustment for age, BMI, and waist circumference. The adjusted ORs for a 1-SD larger thigh circumference were 0.79 (0.53, 1.19) in men and 0.64 (0.46, 0.93) in women. In contrast with hip and thigh circumferences, waist circumference was positively associated with the incidence of type 2 diabetes in these models (ORs ranging from 1.60 to 2.66).

Conclusion: Large hip and thigh circumferences are associated with a lower risk of type 2 diabetes, independently of BMI, age, and waist circumference, whereas a larger waist circumference is associated with a higher risk. *Am J Clin Nutr* 2003;77:1192–7.

KEY WORDS Hip circumference, thigh circumference, waist-to-hip ratio, waist circumference, BMI, body composition, fat distribution, type 2 diabetes, insulin resistance, the Hoorn Study

INTRODUCTION

Although the dramatic worldwide increase in the incidence of obesity, and consequently in the incidence of type 2 diabetes, has been recognized, the exact etiologic link between these remains unclear. It was observed in the Hoorn Study that the waist-to-hip ratio (WHR) and not body mass index (BMI) is an important independent predictor of incident diabetes in 50–75-y-olds (1). This result indicates that fat distribution may be a better predictor for progression to type 2 diabetes than is BMI, which is also suggested by studies that examined the WHR or the waist-to-thigh

ratio (WTR) (2–6). In particular, the accumulation of visceral fat is assumed to play an important role in the etiology of diabetes by overexposing the liver to free fatty acids, resulting in insulin resistance and hyperinsulinemia (7–9).

Evidence, however, that the strong predictive value of the WHR or WTR for type 2 diabetes is not solely due to abdominal fat accumulation (as indicated by waist circumference) is growing. Cross-sectional studies showed that a larger hip circumference is associated with a lower prevalence of self-reported type 2 diabetes and lower fasting glucose concentrations, independently of BMI and waist circumference (10, 11). We obtained similar results in the Hoorn Study for both hip and thigh circumferences (12).

In one prospective study of Chinese men and women, hip circumference was positively associated with the incidence of type 2 diabetes (13). In that study, however, neither waist circumference nor BMI was taken into account. To our knowledge, only one prospective study of the specific association of hip circumference with the incidence of diabetes has been carried out in whites. That study found a larger hip circumference to be associated with a lower incidence of several cardiovascular endpoints and diabetes, independently of waist circumference (14). However, the latter study was limited to women and in both prospective studies the presence of diabetes was not examined on the basis of an oral-glucose-tolerance test (OGTT).

In the Hoorn Study, a population-based cohort study of glucose tolerance, both men and women were included and a 75-g OGTT was performed. The aim of the present study was to investigate the associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes and with

TABLE 1
Baseline characteristics of the men and women[1]

	Men (n = 619)	Women (n = 738)
Age (y)	60.2 ± 6.9	60.4 ± 6.9
BMI (kg/m^2)	25.9 ± 2.7[2]	26.5 ± 3.5
WHR	0.94 ± 0.06[2]	0.83 ± 0.07
WTR	1.68 ± 0.15[2]	1.46 ± 0.16
Waist circumference (cm)	94.2 ± 8.4[2]	85.8 ± 9.9
Hip circumference (cm)	100.2 ± 5.1[2]	102.9 ± 6.9
Thigh circumference (cm)	56.6 ± 4.6[2]	59.6 ± 5.2
Fasting glucose (mmol/L)	5.46 ± 0.49[2]	5.31 ± 0.53
Postload glucose (mmol/L)	5.22 ± 1.65[2]	5.54 ± 1.59

[1] $\overline{x}$ ± SD. WHR, waist-to-hip ratio; WTR, waist-to-thigh ratio.
[2] Significantly different from women, $P < 0.05$ (Student's t test).

changes in fasting and postload glucose concentrations during ≈6 y of follow-up.

SUBJECTS AND METHODS

Subjects

The Hoorn Study is a population-based cohort study of glucose tolerance among 2484 white men and women aged 50–75 y that started in 1989 and has been described elsewhere (15). In 1996–1998 a follow-up examination was carried out. Of the 2484 subjects, 150 subjects had died and 108 subjects had moved out of Hoorn. Another 140 subjects were not invited because of logistic reasons. Of the remaining 2086 subjects who were invited to the follow-up examination, 1513 subjects (72.5%) participated. After the exclusion of subjects with type 2 diabetes at baseline (49 men and 44 women) and subjects with missing anthropometric data, prospective analyses were performed in 1357 subjects (619 men and 738 women). Informed consent was obtained from all participants, and ethical approval for the study was obtained from the local ethics committee.

Measurements

Fasting glucose concentrations and postload glucose concentrations 2 h after a 75-g OGTT were measured in plasma (mmol/L) with the glucose dehydrogenase method (Merck, Darmstadt, Germany) at baseline (15) and with the hexokinase method (Boehringer Mannheim, Mannheim, Germany) at follow-up, except in subjects who were already known to have diabetes. Fasting and postload glucose concentrations were used to classify subjects according to the 1999 World Health Organization criteria (16).

Weight and height were measured while subjects were barefoot and wearing light clothes only, and BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest, and hip circumference was measured at the widest level over the greater trochanters. Thigh circumference was measured on the left leg directly below the gluteal fold. The mean value of 2 measurements was used in the analyses. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference, and waist-to-thigh ratio (WTR) was calculated as waist circumference divided by thigh circumference.

Information on lifestyle factors was obtained by questionnaire. Smoking was expressed in cigarette-years (number of cigarettes smoked per day times the number of years smoked) for smokers or former smokers. Alcohol intake was categorized in 4 groups: nondrinkers and drinkers of ≤10, 10–30, and >30 g/d. Habitual physical activity was expressed as hours per day. The activities included sports, bicycling, gardening, walking, odd jobs, and housekeeping.

Statistical analysis

Differences in baseline characteristics between men and women were tested by Student's t test for normally distributed variables and by Mann-Whitney's test for variables with a skewed distribution. Differences in proportions were tested by the chi-square test.

Logistic regression analyses were performed to study the association of baseline anthropometric measures (BMI, WHR, WTR, and waist, hip, and thigh circumferences) with the incidence of type 2 diabetes. Associations are expressed as odds ratios (ORs) with their 95% CIs per (sex-specific) 1-SD increase in the anthropometric variable involved. An OR can be interpreted as a relative risk. All models were adjusted for age and then additionally for baseline glucose concentrations. The influence of possible confounding by lifestyle factors was studied by adding these factors to the regression model. Possible interaction (effect modification) by sex, age, and anthropometric characteristics was studied by adding product terms to the model. Because the follow-up duration was not the same for each individual, we repeated the analyses with additional adjustment for follow-up duration.

To use cutoffs for fasting and postload glucose concentrations and combine them for the definition of type 2 diabetes (16) implicates a loss of quantitative information. To examine whether the results of the logistic regression analyses for hip, thigh, and waist circumferences were influenced by the use of these criteria, linear regression analyses were performed with continuous fasting and continuous postload glucose concentrations at follow-up as the outcome variables. These regression models were adjusted for age and BMI and then additionally for baseline fasting or postload glucose concentrations. Standardized β coefficients are reported to make the regression coefficients directly comparable between the different anthropometric measures. A standardized β of 0.1 indicates that if the independent variable changes 1 SD, the dependent variable changes 0.1 SD. The stability of the models was considered to be disturbed by multicolinearity if tolerance was <0.1. Tolerance is a statistic used to determine how much the independent variables are linearly related to one another. It is calculated as $1 - R^2$ for an independent variable when it is predicted by the other independent variables already included in the analyses. All analyses were performed by using SPSS for WINDOWS (version 10.1.0; SPSS Inc, Chicago).

RESULTS

Baseline characteristics by sex are shown in **Table 1**. The men and women were of the same age, but differed significantly in all anthropometric measures: the women had higher BMI and thigh and hip circumferences, but lower waist circumference, WHR, and WTR. The men had higher fasting glucose concentrations, whereas the women had higher postload glucose concentrations, although the differences in glucose concentrations were relatively small. Follow-up duration did not differ significantly between the men and women (6.4 ± 0.5 y in both sexes), and ranged from 4.4 to 8.1 y in men and from 4.5 to 7.9 y in women. The women were more physically active, smoked less, and had a lower alcohol intake than did the men (data not shown).

TABLE 2
Relative risk [odds ratio (OR)] for the development of type 2 diabetes per 1-SD increase in risk factor: logistic regression analyses[1]

Risk factors in model[2]	Men (n = 619) OR (95% CI)	Women (n = 738) OR (95% CI)
Model 1: BMI	1.03 (0.79, 1.34)	1.53 (1.21, 1.95)[3]
Model 2: WHR	1.55 (1.17, 2.06)[3]	2.15 (1.63, 2.83)[3]
Model 3: BMI	0.79 (0.57, 1.08)	1.20 (0.91, 1.58)
WHR	1.75 (1.27, 2.41)[3]	1.98 (1.47, 2.67)[3]
Model 4: Waist circumference	1.23 (0.95, 2.64)	1.98 (1.54, 2.55)[3]
Model 5: Hip circumference	0.87 (0.66, 1.14)	1.27 (1.00, 1.62)[4]
Model 6: Waist circumference	1.94 (1.31, 2.88)[3]	2.75 (1.90, 3.97)[3]
Hip circumference	0.54 (0.36, 0.79)[3]	0.65 (0.45, 0.92)[4]

[1] WHR, waist-to-hip ratio.
[2] All models were adjusted for age.
[3] P < 0.01.
[4] P < 0.05.

TABLE 3
Relative risk [odds ratio (OR)] for the development of type 2 diabetes per 1-SD increase in risk factor: logistic regression analyses[1]

Risk factors in model[2]	Men (n = 619) OR (95% CI)	Women (n = 738) OR (95% CI)
Model 1: BMI	1.03 (0.79, 1.34)	1.53 (1.21, 1.95)[3]
Model 2: WTR	1.41 (1.05, 1.89)[4]	2.08 (1.59, 2.72)[3]
Model 3: BMI	0.97 (0.73, 1.27)	1.31 (1.02, 1.69)[4]
WTR	1.42 (1.05, 1.92)[4]	1.92 (1.45, 2.54)[3]
Model 4: Waist circumference	1.23 (0.95, 2.64)	1.98 (1.54, 2.55)[3]
Model 5: Thigh circumference	0.90 (0.68, 1.19)	1.00 (0.79, 1.28)
Model 6: Waist circumference	1.44 (1.05, 1.96)[4]	2.37 (1.78, 3.17)[3]
Thigh circumference	0.73 (0.52, 1.04)	0.68 (0.50, 0.92)[4]

[1] WTR, waist-to-thigh ratio.
[2] All models were adjusted for age.
[3] P < 0.01.
[4] P < 0.05.

During follow-up, 64 men (10.3%) and 68 women (9.2%) developed type 2 diabetes. Type 2 diabetes was diagnosed by a general practitioner in only 6 men and 12 women before the follow-up examination took place; the remaining patients were diagnosed at this examination. Because sex was a significant effect modifier in the relation between anthropometry and incident diabetes, we performed all analyses for men and women separately. The results in **Table 2** show that after adjustment for age, WHR was a strong predictor for type 2 diabetes in both sexes (model 2), whereas BMI was a significant predictor in women only (model 1). After mutual adjustment (model 3), only WHR seemed to be important in predicting diabetes. Waist circumference (model 4) was less strongly associated with incident diabetes after adjustment for age than was the WHR, suggesting a predictive role for hip circumference.

To examine whether the association of WHR was largely due to waist circumference or to hip circumference, we added these variables separately into one regression model (model 6). After adjustment for BMI also, both circumferences appeared to be significantly associated in opposite directions with the risk of diabetes in both sexes (**Figure 1**). BMI was not significantly associated with the incidence of type 2 diabetes in this model. No interactions were observed between anthropometric variables or between age and anthropometric variables. Similar analyses were performed for the WTR and thigh circumference (**Table 3**). The results were similar, except that in men, thigh circumference was not significantly associated with a lower risk of diabetes (model 6). Adjustment for BMI did not change this result (**Figure 2**). Adjustment for lifestyle factors (smoking, alcohol intake, and physical activity) also did not change the results (data not shown).
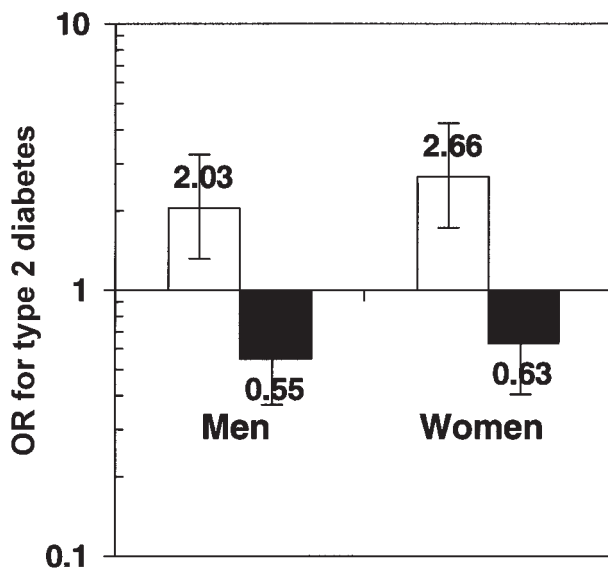

FIGURE 1. Odds ratios (ORs) for developing type 2 diabetes per 1-SD larger waist (□) and hip (■) circumferences. Waist circumference was adjusted for hip circumference, BMI, and age; hip circumference was adjusted for waist circumference, BMI, and age.
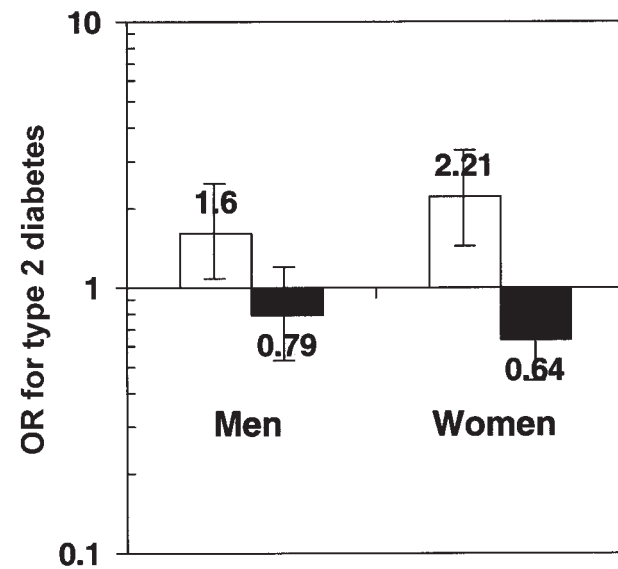

FIGURE 2. Odds ratios (ORs) for developing type 2 diabetes per 1-SD larger waist (□) and thigh (■) circumferences. Waist circumference was adjusted for thigh circumference, BMI, and age; thigh circumference was adjusted for waist circumference, BMI, and age.

TABLE 4
Associations (standardized β coefficients) of baseline body circumferences with continuous fasting glucose concentrations at follow-up: multiple linear regression analyses

Independent variables	Men (n = 619)		Women (n = 738)	
	β	P	β	P
Model 1[1]				
Waist circumference	0.284	0.000	0.216	0.000
Hip circumference	−0.178	0.005	−0.154	0.008
Model 2[1]				
Waist circumference	0.219	0.001	0.157	0.011
Thigh circumference	−0.036	0.528	−0.134	0.005
Model 3[2]				
Waist circumference	0.159	0.008	0.094	0.082
Hip circumference	−0.102	0.064	−0.076	0.134
Model 4[2]				
Waist circumference	0.120	0.036	0.060	0.267
Thigh circumference	−0.024	0.633	−0.084	0.043

[1] Adjusted for age and BMI.
[2] Adjusted for age, BMI, and baseline fasting glucose concentration.

TABLE 5
Associations (standardized β coefficients) of baseline body circumferences with continuous postload glucose concentrations at follow-up: multiple linear regression analyses

Independent variables	Men (n = 619)		Women (n = 738)	
	β	P	β	P
Model 1[1]				
Waist circumference	0.203	0.003	0.253	0.000
Hip circumference	−0.180	0.005	−0.203	0.000
Model 2[1]				
Waist circumference	0.137	0.036	0.182	0.003
Thigh circumference	−0.037	0.517	−0.148	0.002
Model 3[2]				
Waist circumference	0.083	0.162	0.119	0.021
Hip circumference	−0.074	0.180	−0.057	0.240
Model 4[2]				
Waist circumference	0.056	0.322	0.093	0.072
Thigh circumference	−0.007	0.889	−0.066	0.097

[1] Adjusted for age and BMI.
[2] Adjusted for age, BMI, and baseline postload glucose concentration.

The ORs for a 1-SD larger hip circumference after adjustment for waist circumference and all lifestyle factors were 0.52 (95% CI: 0.33, 0.80) for men and 0.65 (95% CI: 0.43, 0.98) for women. A 1-SD larger thigh circumference after adjustment for waist circumference and all lifestyle factors resulted in ORs of 0.80 (95% CI: 0.53, 1.20) for men and 0.64 (95% CI: 0.44, 0.93) for women. Adjustment for follow-up duration did not change any of the observed associations (data not shown). After adjustment for baseline fasting and postload glucose concentrations, only waist circumference in women remained significantly associated with the incidence of type 2 diabetes (data not shown).

The results of the multiple linear regression models for the associations of baseline body circumferences with follow-up fasting and postload glucose concentrations are shown in **Tables 4** and **5**, respectively. We adjusted for age and BMI (models 1 and 2) and then additionally for baseline fasting or postload glucose concentrations (model 3 and 4). In accordance with the results of the logistic regression analyses, glucose concentrations (fasting and postload) were positively associated with baseline waist circumference and negatively associated with baseline hip or thigh circumference, although the results were not significant for thigh circumference in men (models 1 and 2). After adjustment for baseline glucose concentrations (models 3 and 4), most associations became nonsignificant: in men, waist circumference was still significantly and positively associated with fasting glucose, whereas in women only thigh circumference was significantly associated (negatively). None of the circumferences was significantly associated with postload glucose concentrations in men, whereas in women waist circumference was positively associated and thigh circumference was negatively associated after adjustment for baseline postload glucose concentrations.

The correlation between waist and hip circumferences was 0.71 in men and 0.69 in women, and the correlation between waist and thigh circumferences was 0.46 in men and 0.42 in women. The regression models were not disturbed by multicolinearity.

DISCUSSION

In the present study, we showed that the body circumference ratios (WHR and WTR) are better predictors of future type 2 diabetes than is overall obesity measured by BMI. Both waist and hip circumference have important, but opposite, associations with the risk of diabetes after adjustment for age and BMI. A larger waist circumference is associated with a higher risk of diabetes, whereas a larger hip circumference is associated with a lower risk of diabetes. A larger thigh circumference was also associated with a lower risk of diabetes, although the protective effect was statistically significant only in women. The measurements of continuous glucose concentrations showed that fasting and postload concentrations were positively associated with baseline waist circumference and negatively associated with baseline hip and thigh circumferences.

Of the 2086 persons who were invited for the follow-up examination, 72.5% participated. These participants were healthier at baseline than were the nonparticipants (1). Therefore, it is possible that we underestimated the true incidence of diabetes and consequently underestimated the associations with waist, hip, and thigh circumferences.

When incident diabetes or continuous glucose concentrations after follow-up are used as the study outcome, there is often discussion of whether to adjust for baseline glucose concentrations. Adjustment for baseline glucose answers the question of whether knowledge about the thigh or hip circumference contributes to the prediction of incident diabetes once baseline glucose is taken into account. In our study, thigh or hip circumference did not independently contribute to incident diabetes or continuous glucose concentrations after adjustment for baseline glucose. However, if baseline glucose concentrations and baseline thigh or hip circumferences result from the same etiologic process, adjustment for glucose concentrations would be inappropriate. Alternatively, if we assume that there is a causal association of thigh or hip circumference with impaired glucose metabolism, it is possible that persons with narrow hips or small thighs had increased glucose concentrations already at baseline. If we then adjust for these baseline glucose concentrations, the effects of thigh or hip circumference disappear. The observed cross-sectional association between body circumferences and glucose concentrations (12) reinforce these suggestions. Waist circumference is more likely to remain a significant predictor of type 2 diabetes after adjustment for baseline glucose concentrations.

Our observation that central obesity, independent of overall obesity, is an important determinant of type 2 diabetes is not new (3–6). The abdominal visceral fat is considered to be possibly etiologically important through increased fatty acid release into the portal system (7–9). Our results extend these findings by showing an independent association of waist and hip circumferences with the development of diabetes. Our results agree with the results of the scarce cross-sectional studies (10, 11). One previous prospective study, showing an independent protective effect of hip circumference on the development of diabetes, was limited to women (14). Furthermore, the presence of diabetes was examined on the basis of an OGTT. In the present prospective study, an OGTT was performed in both men and women. In addition, we included measurements of thigh as well as hip circumference.

The negative association of hip circumference with glucose metabolism was proposed to be caused by a greater muscle mass at the gluteal region (10). Muscle mass is one of the sites of insulin resistance as well as the main target of insulin. WHR has been related to both larger visceral fat and smaller leg muscle areas in men (17). Also, the higher prevalence of glucose tolerance in Indian men than in Swedish men was related to lower muscle mass (18). Thigh circumference might better reflect muscle mass than hip circumference, because it is less likely to be influenced by frame size (pelvic width). Our results, however, show that hip circumference has a stronger negative association with glucose concentrations than does thigh circumference, especially in men.

Larger thigh and hip circumferences could also reflect increased femoral and gluteal subcutaneous fat mass. Particularly in women, these depots have relatively high lipoprotein lipase activity and relatively low rates of basal and stimulated lipolysis (19). These depots may protect the liver and muscle from high exposure to free fatty acids through uptake and storage. Recently, Van Pelt et al (20) showed that larger leg fat mass measured by dual-energy X-ray absorptiometry was associated with better insulin sensitivity and a better lipid profile after adjustment for trunk fat.

Regional differences in adipocyte metabolism (lipoprotein lipase activity and lipolysis) are more pronounced in women than in men (19). This may explain why the observed protective role of larger thighs was stronger in the women than in the men in the present study. Furthermore, the interpretation of hip circumference may differ between men and women. Gluteal fat mass and pelvic width may be the main determinants of hip circumference in women, whereas pelvic width and muscle mass may be the main determinants in men.

Adrenal and sex steroid concentrations and growth hormone concentrations may influence visceral fat accumulation as well as the development of insulin resistance (21–24). For example, hyperandrogenicity in women and hypoandrogenicity in men has been associated with insulin sensitivity and the development of type 2 diabetes (25, 26) and with fat distribution (27–29). These steroids may influence adipose tissue by changing lipoprotein lipase activity (7, 22, 25, 30). In the present study, no information on hormones was available.

Although the exact mechanisms need to be further explored, the results of the present study show that body tissue distribution is an important factor in the development of type 2 diabetes in older persons, even more than is BMI. Therefore, lifestyle interventions aimed at the prevention of type 2 diabetes not only should focus on weight loss but should preferably combine approaches that decrease waist circumference and increase hip or thigh circumference. Increased physical activity, less heavy drinking, and smoking cessation have been shown to do both (31). Energy restriction tends to decrease both waist and hip or thigh circumference. Increased physical activity results in a better body composition, by an increase of the muscle mass in the legs and a decrease in visceral fat accumulation. The better body composition achieved by smoking cessation and less heavy drinking is suggested to be caused by the influence these have on hormones, as discussed above. Further research on prevention strategies, however, is needed.

In summary, larger hip or thigh circumference is associated with a lower risk of type 2 diabetes in both men and women, independently of BMI, age, and waist circumference, whereas larger waist circumference is associated with higher risk. Further research should be aimed at determining the underlying etiologic mechanisms of this association and whether our results can be extrapolated to other ethnic groups.

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