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Body Fat Distribution and Risk of Non-Insulin-dependent Diabetes Mellitus in Women

The Nurses' Health Study

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Obesity is an established risk factor for non-insulin-dependent diabetes mellitus (NIDDM). Anthropometric measures of overall and central obesity as predictors of NIDDM risk have not been as well studied, especially in women. Among 43,581 women enrolled in the Nurses' Health Study who in 1986 provided waist, hip, and weight information and who were initially free from diabetes and other major chronic diseases, NIDDM incidence was followed from 1986 to 1994. After adjustment for age, family history of diabetes, smoking, exercise, and several dietary factors, the relative risk of NIDDM for the 90th percentile of body mass index (BMI) (weight (kg)/height (m)^2) (BMI = 29.9) versus the 10th percentile (BMI = 20.1) was 11.2 (95% confidence interval (CI) 7.9–15.9). Controlling for BMI and other potentially confounding factors, the relative risk for the 90th percentile of waist : hip ratio (WHR) (WHR = 0.86) versus the 10th percentile (WHR = 0.70) was 3 1 (95% CI 2.3–4.1), and the relative risk for the 90th percentile of waist circumference (36.2 inches or 92 cm) versus the 10th percentile (26.2 inches or 67 cm) was 5.1 (95% CI 2.9–8.9). BMI, WHR, and waist circumference are powerful independent predictors of NIDDM in US women. Measurement of BMI and waist circumference (with or without hip circumference) are potentially useful tools for clinicians in counseling patients regarding NIDDM risk and risk reduction. *Am J Epidemiol* 1997;145:614–19.

body composition; body constitution; body weight; diabetes mellitus, non-insulin-dependent; obesity

Non-insulin-dependent diabetes mellitus (NIDDM) is a major health problem in the United States. Physiologic data demonstrate greater insulin resistance and glucose intolerance among the obese (1), and a number of prospective studies support associations between measures of obesity and NIDDM risk. Body mass index (BMI) has been found to be a powerful predictor of NIDDM in studies of both men (2–6) and women (2, 4, 7, 8). Central obesity has also been identified as an important determinant of NIDDM risk. A nested case-control study of US women by Kaye et al. (7) found that after adjustment for BMI, age, and education, women with NIDDM were 4.6 times as likely to be in the highest rather than the lowest tertile of waist : hip ratio (WHR) (95 percent confidence interval 3.8–5.6). The Gothenburg Study also found various measures of central fat distribution and BMI to be independently and simultaneously correlated with NIDDM risk (8).

Prospective data from the Nurses' Health Study, a large cohort study involving over 121,700 women, provide a basis for a better understanding of the role of obesity in NIDDM. A strong association between baseline BMI and risk of developing NIDDM was previously reported in this cohort (9, 10). The present study evaluates the magnitude of NIDDM risk over 8 years of follow-up as a function of several anthropometric measures of obesity, including BMI, waist circumference, and WHR.

MATERIALS AND METHODS

Sample

The Nurses' Health Study cohort was formed in 1976 when 121,701 female registered nurses aged

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Abbreviations: BMI, body mass index; NIDDM, non-insulin-dependent diabetes mellitus, WHR, waist : hip ratio.

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TABLE 1. Age-adjusted* models of NIDDM† risk, according to three different anthropometric indices of overall and central obesity: Nurses' Health Study, 1986–1994

Categories	No of cases	Person-years of observation	RR† (95% CI†)	*p* for trend
Model I: body mass index‡				
<21	21	63,317	1.0	
21–22.9	40	82,395	1.2 (0.8–1.7)	
23–24.9	82	73,042	3.1 (2.1–4.5)	
25–26.9	90	45,066	7.0 (4.9–10.1)	
27–28.9	96	27,775	9.6 (6.8–13.7)	
29–30.9	112	17,970	12.7 (8.9–18.0)	
≥31	264	23,819	18.1 (12.8–25.7)	<0.0001
Model II: waist:hip ratio				
<0.72	28	55,216	1.0	
0.72–0.75	56	87,595	0.9 (0.8–1.2)	
0.76–0.79	120	78,573	2.9 (2.3–3.8)	
0.80–0.83	176	59,266	6.3 (4.8–8.2)	
0.84–0.87	135	30,974	6.9 (5.3–9.0)	
≥0.88	190	21,760	7.5 (5.7–9.8)	<0.0001
Model III: waist circumference (inches)				
<28 (<71)§	16	73,745	1.0	
28–29 (71–75.9)	44	77,245	1.6 (1.0–2.6)	
30–31 (76–81)	62	62,418	4.6 (3.0–7.1)	
32–33 (81.1–86)	117	47,473	8.7 (5.7–13.2)	
34–35 (86.1–91)	99	30,422	12.1 (8.0–18.4)	
36–37 (91.1–96.3)	109	18,952	16.7 (11.1–25.3)	
≥38 (≥96.4)	258	23,129	22.4 (14 8–33.9)	<0.0001

* Age adjustment was relative to the age distribution of the Nurses' Health Study cohort.
† NIDDM, non-insulin-dependent diabetes mellitus; RR, relative risk; CI, confidence interval.
‡ Weight (kg)/height (m)^2.
§ Numbers in parentheses, centimeters.

30–55 years and living in 11 US states returned a mailed questionnaire (11, 12). These women have been queried every 2 years on risk factors and health outcomes, including diagnosis of diabetes mellitus. In 1986, 83,477 participants returned a questionnaire that requested information on current weight and self-measured body circumferences, and 51,008 respondents provided this information. From this subset, we excluded women with prevalent cancer, heart disease, stroke, or diabetes; women with incident type I diabetes or incident gestational diabetes; women with incident unconfirmed NIDDM; and women with outlying or missing values for major risk factors. This left 43,581 women for age-adjusted analyses. Further exclusions due to missing data on important confounders yielded the complete data subcohort (n = 42,492).

Diabetes confirmation and validation

All women who reported a physician diagnosis of diabetes on the biennial questionnaire were mailed a supplemental questionnaire about symptoms, laboratory results, and treatment. Participants with a self-report of diabetes mellitus were considered to have type II (non-insulin-dependent) diabetes if they did not meet criteria for type I (insulin-dependent) diabetes and met the National Diabetes Data Group criteria for NIDDM (13). No weight criterion was used in NIDDM classification.

The validity of diabetes ascertainment was assessed by examination of medical records in a random sample of 84 women (14). Reports were positively confirmed in 98 percent of cases.

Anthropometric variables and validation

BMI was calculated as 1986 weight (kg) divided by the square of 1976 height (m^2) (9). The main 1986 questionnaire requested that the participant's waist and hips be measured at the point of greatest circumference while the participant stood in a relaxed stance. Only measured, not estimated, values were to be recorded. Self-reported weight has been shown to be valid in this cohort (15). The validity of circumference self-reports in this cohort was examined by Rimm et al. (16), who concluded that moderate but nondifferential measurement error was present.

TABLE 2. Multivariate models of NIDDM* risk controlling for combinations of anthropometric indices of overall and central obesity and potentially confounding factors†: Nurses' Health Study, 1986–1994

Categories	RR* (95% CI*)	p for trend
Model I: body mass index‡		
<21	1.0	
21–22.9	1.2 (0.8–1.6)	
23–24.9	2.9 (2.0–4.3)	
25–26.9	6.5 (4.6–9.4)	
27–28.9	8.8 (6.2–12.5)	
29–30.9	11.4 (8.0–16.2)	
≥31	15.9 (11.2–22.6)	<0.0001
Model II: body mass index and waist.hip ratio		
Body mass index		
<21	1.0	
21–22 9	1.1 (0.8–1.5)	
23–24.9	2.3 (1.6–3.3)	
25–26.9	4 4 (3.1–6.4)	
27–28.9	5.8 (4 0–8.3)	
29–30.9	7.4 (5.1–10.6)	
≥31	10.1 (7.0–14.5)	<0.0001
Waist:hip ratio		
<0.72	1.0	
0.72–0.75	1.0 (0.8–1.2)	
0.76–0.79	1.9 (1.5–2 4)	
0.80–0.83	2.9 (2.2–3.8)	
0.84–0.87	3.1 (2.3–4.1)	
≥0.88	3.3 (2.5–4.3)	<0.0001
Model III: body mass index and waist circumference		
Body mass index		
<21	1.0	
21–22.9	0.9 (0.6–1.3)	
23–24.9	1.5 (0.9–2.3)	
25–26.9	2.3 (1.4–3.8)	
27–28.9	2 7 (1.7–4.5)	
29–30.9	3.2 (1.9–5.2)	
≥31	3.8 (2.3–6 3)	<0 0001
Waist circumference (inches)		
<28 (<71)§	1.0	
28–29 (71–75.9)	1.4 (0.8–2.3)	
30–31 (76–81)	2.7 (1.6–4.6)	
32–33 (81.1–86)	3.9 (2.2–6.8)	
34–35 (86.1–91)	4.6 (2.6–8.0)	
36–37 (91.1–96.3)	5.4 (3.1–9.4)	
≥38 (≥96.4)	6.2 (3.5–11.0)	<0.0001

* NIDDM, non-insulin-dependent diabetes mellitus; RR, relative risk; CI, confidence interval

† Confounders included in all models: age, family history of diabetes, exercise, smoking, intakes of saturated fat, calcium, potassium, and magnesium, and glycemic index.

‡ Weight (kg)/height (m)^2.

§ Numbers in parentheses, centimeters.

Covariates

Information on all covariates for these analyses was obtained from the 1986 questionnaire, except that for family history of diabetes, collected in 1982, and height, collected in 1976. Physical activity is represented as a metabolic equivalent score derived from reports of weekly activities (17, 18). Dietary variables associated with NIDDM risk include measures of alcohol (g/day), saturated fat (g/day), calcium (mg/day), magnesium (mg/day), and potassium (mg/day) intakes and an energy-adjusted glycemic index (Jorge Salmeron, Harvard School of Public Health, personal communication, 1995) obtained from a semiquantitative food frequency questionnaire (19). Family history of NIDDM is considered positive if a participant reports that a first degree relative ever had diabetes. With regard to smoking, individuals were classified as a never smoker, a past smoker, or a current smoker in one of three categories of cigarettes smoked per day (1–14, 15–24, and ≥25).

Data analysis

All BMI values greater than 48.9 were excluded as "GESD outliers" (20). Subjects reporting waist measurements greater than 55 inches or less than 15 inches and hip measurements greater than 65 inches or less than 20 inches also were excluded.

Person-years of follow-up were calculated as the time from completion of the 1986 questionnaire to the date of return of the 1994 questionnaire or the date of diagnosis of NIDDM. Age-adjusted rates were standardized to the age distribution of the entire Nurses' Health Study cohort.

NIDDM risk gradients for each fat distribution measure were estimated using proportional hazards models. Restricted cubic spline transformations (21, 22) with knots at quintiles of obesity measures were used to flexibly model relations between continuous body fat distribution measures and NIDDM risk. Estimated relative risks and 95 percent pointwise confidence intervals are functions of fitted spline coefficients, and are reported for each risk factor using the 10th percentile value of the factor as the reference.

RESULTS

Univariate and multivariate hazard models

Table 1 presents raw data and age-adjusted relative risks of NIDDM for BMI, waist circumference, and WHR. Strong positive associations are revealed between all of the obesity measures and NIDDM risk, with waist circumference yielding the sharpest risk gradient (38.8 inches (98.5 cm) vs. 26.3 inches (66.8 cm): relative risk = 22.4, 95 percent confidence interval 14.8–33.9).

Table 2 presents multivariate relative risks derived from models in which adjustments were made for

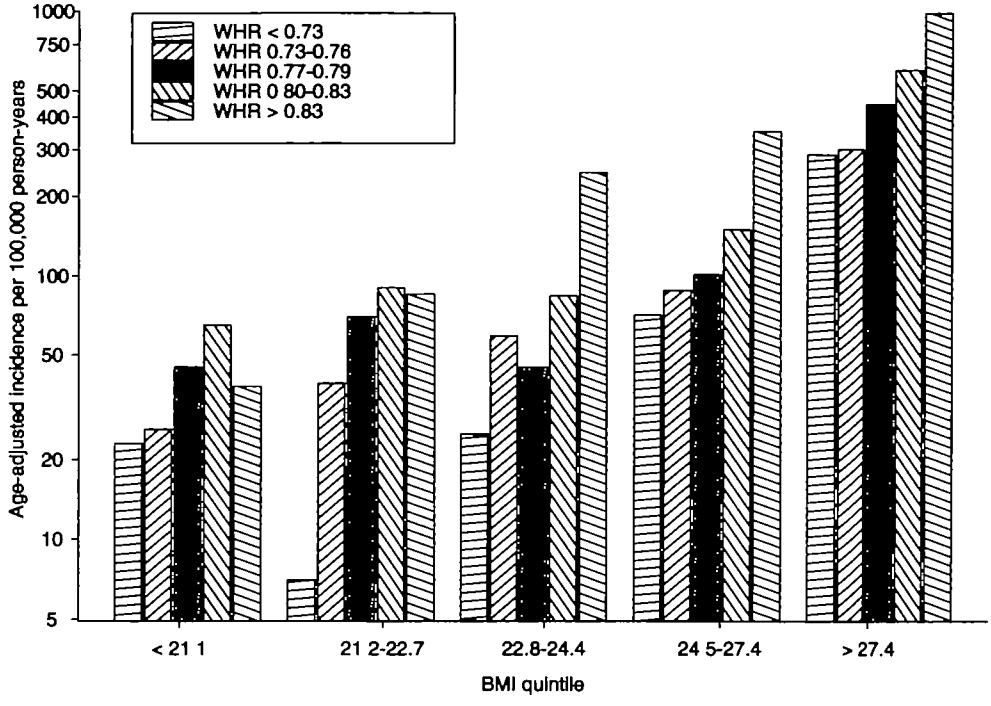

FIGURE 1. Age-adjusted incidence rates of non-insulin-dependent diabetes mellitus per 100,000 person-years (standardized to the age distribution of the Nurses' Health Study cohort), cross-classified according to quintile of body mass index (BMI) and waist · hip ratio (WHR). The cross-hatching on the bars identifies the WHR quintiles according to the boxed key in each plot.

potential confounders of the relation between obesity and NIDDM. The BMI-NIDDM risk relation remained strong after adjustment for age, family history of diabetes, exercise, smoking, intakes of saturated fat, calcium, potassium, and magnesium, and glycemic index. The estimated relative risk function increased monotonically with increasing BMI, and even levels of BMI not considered to indicate obesity (BMI = 23–24.9) were associated with significantly elevated NIDDM risk. Models 2 and 3 of table 2 assessed simultaneous effects of BMI and central obesity measures, controlling for all available confounders. All anthropometric factors were strongly monotonically associated with NIDDM risk in simultaneous modeling. The results of Wald-type trend tests for all factors were highly significant ($p < 0.0001$ in each case). The estimated effect of BMI was attenuated (but the significance of the association was not eliminated) when data were adjusted simultaneously for central obesity. The attenuation is much more pronounced in model 3 of table 2 than in model 2, reflecting the high correlation (crude $r = 0.81$) between BMI and waist circumference.

Effect modification

Figures 1 and 2 present age-adjusted NIDDM incidence estimates within 5 × 5 cross-classifications based on WHR × BMI and waist × BMI quintiles. Figure 1 shows that, with some qualification in the lowest BMI quintile (probably due to data sparsity), there was, for each stratum of BMI, a consistent increase in NIDDM risk as WHR increased. A formal test for interaction between BMI level and WHR-associated NIDDM risk gradient gave a nonsignificant p value ($p = 0.11$). Essentially the same interpretation follows for waist size (figure 2). There was a consistent increase in NIDDM risk as waist size increased within each BMI category. The p value from the test for interaction was nonsignificant ($p = 0.21$). It is also noteworthy that a high BMI was a strong predictor of NIDDM even among women with a low WHR or a low waist circumference; and, likewise, greater central obesity increased NIDDM risk at all BMI levels.

DISCUSSION

The present data indicate that various anthropometric measures, including BMI, waist circumference, and WHR, are each independent determinants of NIDDM risk in this cohort of US women. Previous studies have suggested that measures of central adiposity might provide additional information on NIDDM risk beyond that provided by BMI only in the upper extremes of marginal central obesity distributions. After fine adjustment for BMI, a 5-year longitudinal study of US

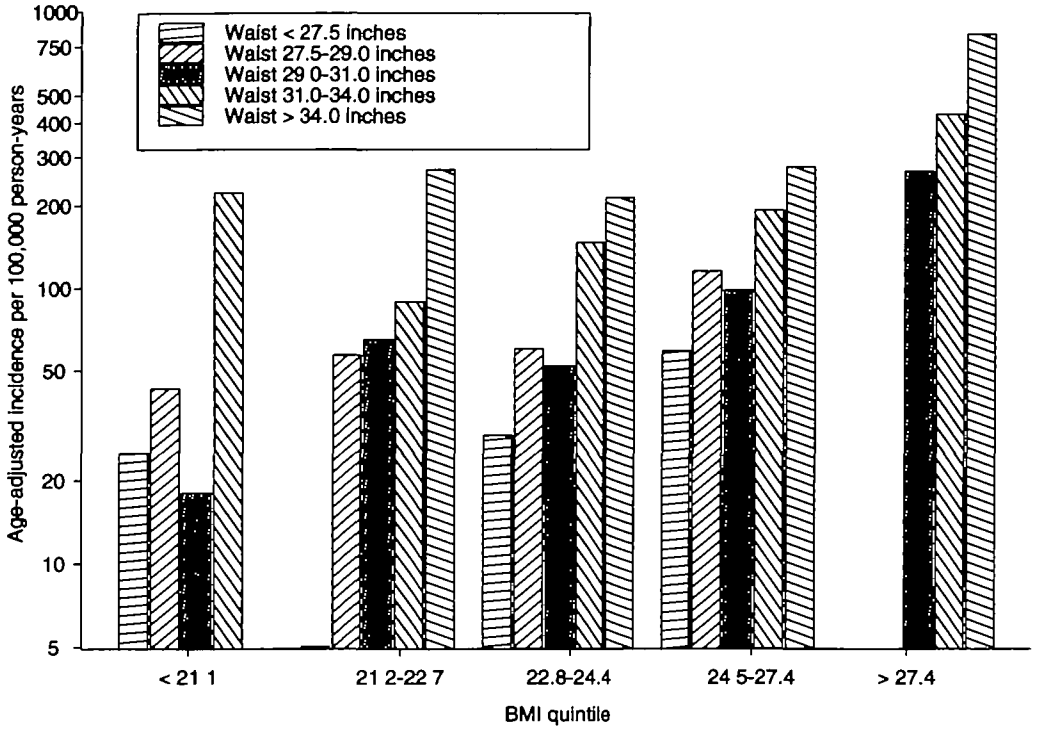

FIGURE 2. Age-adjusted incidence rates of non-insulin-dependent diabetes mellitus per 100,000 person-years (standardized to the age distribution of the Nurses' Health Study cohort), cross-classified according to quintiles of body mass index (BMI) and waist circumference The cross-hatching on the bars identifies the waist circumference quintiles according to the boxed key in each plot. (Quintiles of waist circumference in centimeters: <69 9, 69 9–73.7, 73.7–78.7, 78 7–86 4, and >86.4).

male health professionals found WHR to be a good predictor of NIDDM in only the top 5 percent of WHR, and waist circumference to be predictive among the top 20 percent (6). A study of Swedish women followed for 12 years reported a sharp increase in risk occurring in the upper 20th percentile of each body fat measure analyzed (8). In contrast, the present data suggest that WHR and waist circumference are independent predictors of NIDDM throughout their observed ranges of values.

Various limitations of this analysis are worthy of note. First, self-reported weight, waist, and hip measures may have been erroneous, introducing misclassification of subjects' risk-factor status into our modeling. Validation studies of self-reported weight, waist, and hip measures were conducted in this cohort (15, 16) and failed to disclose evidence of differential mismeasurement of these quantities by age or technician-measured weight. Furthermore, correction of model 2 of table 2 for measurement error in both BMI and WHR was performed using the methods of Rosner et al. (23). The corrected estimates confirmed that WHR was significantly associated with NIDDM risk after adjustment for BMI and other confounding factors.

A second potential source of concern is the high frequency of nonresponse to questions on the anthropometric measures. It is highly likely that nonresponse is ignorable for the purposes of this prospective analysis. The tendency of a subject to withhold information on these items may depend on their true values, but this tendency is not otherwise informative with regard to the risk of future NIDDM. Our relative risk estimates remain unbiased, and our inferences valid, in this setting.

A third limitation is the possibility of surveillance bias. It is known that prevalent cases of diabetes with minimal or no symptoms sometimes escape detection, and obese subjects might be more likely to be diagnosed with NIDDM. Previous work with this cohort has reported that neither prevalence of reported symptoms at diagnosis nor frequency of physician visits varied according to BMI (24). Our analysis indicates substantially increased risk for women with BMI values $\geq$ 24 and WHR values $\geq$ 0.76; and differential surveillance, while a potential problem in modeling diabetes risk among clearly obese women, is quite unlikely at these levels of body fat measures, which are actually below average. Consequently, we do not believe that surveillance bias poses a substantial threat to the interpretation of these results.

These data provide strong evidence that measures of central obesity based on body circumferences provide important predictive information regarding risk of NIDDM beyond that provided by BMI. Centrally located adipocytes may have specific metabolic roles in the pathogenesis of insulin resistance and NIDDM (25). The relation of central obesity to NIDDM risk described in this and other reports is compatible with these observations, but further research will be needed to clarify the biologic interpretation of the observations reported here. Recent reports document associations of waist circumference with cardiovascular risk factors (26, 27) and describe "action levels" based on waist circumference for clinical encouragement of weight control. We conclude that BMI and waist circumference (with or without hip circumference) are both potentially useful tools for clinicians in counseling patients regarding NIDDM risk and risk reduction.

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