

## Body Fat Distribution and Male/Female Differences in Lipids and Lipoproteins

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**The role of body fat distribution, as assessed by the ratio of waist-to-hip circumferences (WHR), in statistically explaining differences in levels of lipoproteins between men and women was studied using data collected in 1985–1986 from employed adults (mean age, 40 years). As compared with the 415 women, the 709 men had higher mean levels of triglycerides (+38 mg/dl) and apolipoprotein B (+11 mg/dl) as well as lower mean levels of high density lipoprotein (HDL) cholesterol (–15 mg/dl) and apolipoprotein A-I (–19 mg/dl). Additionally, men were more overweight, consumed more alcohol, and exercised more frequently than women but were less likely to smoke cigarettes. Controlling for these characteristics, however, did not alter the differences in lipoprotein levels between men and women. In contrast, adjustment for WHR (which was greater among men) reduced the sex differences in levels of apolipoprotein B (by 98%), triglycerides (by 94%), HDL cholesterol (by 33%), and apolipoprotein A-I (by 21%). Similar results were obtained using analysis of covariance, stratification, or matching; at comparable levels of WHR, differences in lipid and lipoprotein levels between men and women were greatly reduced. Although these results are based on cross-sectional analyses of employed adults and need to be replicated in other populations, the findings emphasize the relative importance of body fat distribution. Whereas generalized obesity and body fat distribution are associated with lipid levels, fat distribution (or a characteristic influencing fat patterning) can be an important determinant of sex differences in levels of triglycerides, HDL cholesterol, and apolipoproteins B and A-I. (*Circulation* 1990;81:1498–1506)**

**W**omen in Westernized countries have a much lower incidence of coronary heart disease than do men.<sup>1,2</sup> Determinants of this sex differential have recently received increased attention,<sup>3,4</sup> and evidence suggests that it might be, in part, because of male/female differences in levels of lipids and lipoproteins. Although the standard risk factors for coronary heart disease are at least as important among women as men,<sup>2,5</sup> relatively low levels of triglycerides and high levels of high density lipoprotein (HDL) cholesterol might protect most women from developing extensive atherosclerosis.

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In contrast, in societies with low rates of coronary heart disease, sex differences in levels of HDL cholesterol,<sup>6</sup> coronary atherosclerosis,<sup>7</sup> and mortality from coronary heart disease<sup>8</sup> are greatly reduced. Furthermore, data from the Framingham Study show that about 15% of the male excess in coronary heart disease among 45–54-year-old subjects can be attributed to levels of total cholesterol and nonlipid risk factors,<sup>5</sup> and sex differences in coronary heart disease are reduced if comparisons are made at similar levels of total/HDL cholesterol.<sup>9</sup> One half of the increased risk of coronary heart disease among men might be because of adverse levels of total cholesterol, glucose, and behavioral characteristics.<sup>10</sup>

Although obesity is an important determinant of lipoprotein levels, the distribution of body fat is also critical.<sup>11</sup> Vague<sup>12</sup> was the first to observe that women with upper-body obesity, the pattern usually seen in men, are more likely to have diabetes and atherosclerosis than are women with lower-body obesity. More recently, body fat distribution, as assessed by various skinfold and circumference measurements, has been related to diabetes and coronary heart disease.<sup>13,14</sup>

Independent of the general overweight level, the ratio of waist-to-hip circumferences (WHR) is associated with adverse levels of lipids, lipoproteins, and insulin,<sup>15,16</sup> and is predictive of coronary heart disease.<sup>17,18</sup>

Although men have higher levels of WHR than women, the role of body fat distribution in explaining male/female differences in levels of lipids and lipoproteins has not been assessed. We have previously shown that WHR is independently related to lipid and lipoprotein levels in men and women.<sup>16</sup> The objective of the present study was to determine whether levels of WHR in this sample can explain the sex differentials in levels of HDL cholesterol, triglycerides, and apolipoproteins A-I and B.

### Methods

#### *Study Population*

Participants were primarily white-collar workers who volunteered for serum lipid screenings at their places of employment (two Milwaukee companies) from June 1985 through March 1986. As previously reported,<sup>16</sup> approximately 50% of all eligible persons participated in these examinations and completed a questionnaire concerning various behavioral characteristics. The majority of participants worked in professional or managerial positions, and men were more likely to take part in the examinations than women. Informed consent was obtained, and the study protocol was approved by the Human Research Review Committee of the Medical College of Wisconsin.

The study was restricted to 1,124 (709 men and 415 women) white 20–69-year-old subjects. Other racial groups represented less than 5% of all participants and were excluded from the analyses, as were 11 persons who had been told by a physician that they were diabetic. Because of their effects on lipoprotein levels, subjects who reported while using lipid-lowering medications ( $n=4$ ) or oral contraceptives ( $n=110$ ) were also excluded.

#### *General Examinations*

Anthropometric measurements were taken in a uniform manner by trained personnel, with participants wearing light clothing during the examination. Weight and height were obtained using calibrated balance scales, and Quetelet index ( $\text{kg}/\text{m}^2$ ) was calculated as a measure of weight relative to height.<sup>19</sup> Waist circumference was measured at the navel, and hip circumference was measured at the widest part of the hips and buttocks. Because circumference measurements were made in inches, this scale is used throughout the analyses.

Information on alcohol intake, smoking, exercise, and oral contraceptive use were obtained from a questionnaire that has been extensively used in patients undergoing coronary arteriography.<sup>20</sup> Usual weekly alcohol intake was expressed as milliliters of absolute alcohol by using values of 4% for beer, 12%

for wine, and 43% for liquor. Exercise was a count of the number of times per month that each person participated in aerobic exercise. Information was not collected on use of postmenopausal hormones; however, analyses were performed to assess the effects of controlling for WHR among subjects who were 50 years old or younger, or more than 50 years old.

#### *Laboratory Analyses*

Ten milliliters of blood were drawn by venipuncture after an overnight fast. Plasma levels of total cholesterol and triglycerides were measured by automated procedures,<sup>21–23</sup> with quality control monitored by the Centers for Disease Control. HDL cholesterol was measured after heparin-manganese precipitation of other lipoproteins, according to procedures developed by the Lipid Research Clinics.<sup>23</sup> The total-to-HDL-cholesterol ratio was used as a measure of the atherogenicity of the lipoprotein profile.

Plasma levels of apolipoprotein B were measured by an enzyme-linked immunoassay<sup>24</sup>; levels were in the range of 22–170 mg/dl, with mean levels of 81 and 70 mg/dl among men and women, respectively. Apolipoprotein A-I was measured by a rate immunonephelometric assay with the Beckman Array-Specific Protein Analysis System<sup>25</sup>; levels were in the range of 74–222 mg/dl (mean, 125 mg/dl) among men and 77–258 mg/dl (mean, 144 mg/dl) among women.

#### *Statistical Methods*

Because the distributions of several variables (e.g., triglycerides) were skewed, various transformations were used. With the exception of one triglyceride value (1,580 mg/dl) that was considered an outlier and was deleted, four missing apolipoprotein B levels, and 17 missing apolipoprotein A-I values, all subjects had recorded levels for the anthropometric, behavioral, and lipid measurements. All  $p$  values are two sided.

Levels of selected characteristics were first contrasted between men and women using Wilcoxon and  $\chi^2$  tests. The coefficient of variation ( $\text{SD} \div \text{mean}$ ) was used to compare the relative variability of WHR and Quetelet index. Interrelations among the anthropometric measures were examined, as was the relation of these variables to lipid and lipoprotein levels. Pearson and Spearman correlations yielded similar results, and only the former are presented.

To assess the relative importance of each anthropometric measurement in explaining the sex differences in lipid and lipoprotein levels, several regression models were constructed. (Because levels of total cholesterol did not differ between men and women, they were not included in these analyses.) Male/female differences in levels of lipids and lipoproteins were assessed using  $F$  tests<sup>26</sup> after adjustment for 1) only the covariates (i.e., age, cigarette smoking, alcohol consumption, and exercise), 2) covariates and Quetelet index, and 3) covariates and

TABLE 1. Mean Levels of Selected Characteristics by Age and Sex

Characteristics	Age group			
	≤40 yr		>40 yr	
	Men (n=414)	Women (n=252)	Men (n=295)	Women (n=163)
Age (yr)	32±5	32±5	50±7	51±7
Total cholesterol (mg/dl)	195±42	187±36	215±43	224±54
Triglycerides (mg/dl)	104±70*	70±33*	137±90*	95±52*
HDL cholesterol (mg/dl)	48±12*	60±14*	47±13*	66±20*
Total/HDL cholesterol	4.3±1.6*	3.3±1.1*	4.9±1.7*	3.6±1.2*
Apo B (mg/dl)	77±21*	65±18*	87±23*	78±24*
Apo A-I (mg/dl)	124±19*	139±23*	127±22*	152±32*
Quetelet index (kg/m <sup>2</sup> )	25.2±3.3*	24.1±4.7*	26.4±3.3†	25.7±5.1†
Waist (in.)	35±4*	29±5*	37±3*	31±5*
Hip (in.)	41±3*	39±4*	42±3*	41±4*
WHR	0.86±0.05*	0.75±0.06*	0.90±0.04*	0.76±0.06*
Alcohol consumption (ml/wk)	125±130*	76±82*	136±146*	75±88*
Exercise (times/wk)	10±9*	7±8*	8±9*	4±6*
Current smoker (%)	13†	23†	16	22

Values are mean±SD. HDL, high density lipoprotein; apo B, apolipoprotein B; apo A-I, apolipoprotein A-I; WHR, waist-to-hip ratio.

\* $p<0.001$ ; † $p<0.01$ .  $p$  values are for equality of means between men and women (within each age group) and were calculated using either Wilcoxon or  $\chi^2$  tests.

WHR. Male/female differences in lipid and lipoprotein levels were also examined within strata of WHR. Additionally, men and women were matched on WHR (to the nearest 0.01), and paired  $t$  tests were used to assess differences in lipoprotein levels among these 118 pairs.

## Results

### Descriptive Characteristics

Mean ages of men and women were similar (men, 40 years; women, 39 years), and levels of selected characteristics are shown in Table 1. With the exception of total cholesterol, all lipid and lipoprotein levels differed significantly between the sexes. Overall, men had higher levels of triglycerides (+38 mg/dl), total/HDL cholesterol (+1.2), and apolipoprotein B (+11 mg/dl) but lower levels of HDL cholesterol (−15 mg/dl) and apolipoprotein A-I (−13 mg/dl). Furthermore, these differences were virtually identical for both age groups, and similar results were obtained by various transformations (e.g., the geometric means for triglycerides differed by 29 mg/dl). Men also consumed more alcohol and exercised more frequently than women; however, a smaller proportion reported smoking cigarettes.

Mean levels of the anthropometric measures were higher in men, with WHR showing the largest (14%) proportional difference. This difference in WHR, together with its low variability (coefficient of variation, 6–8%), resulted in a marked separation of WHR levels

between the sexes (Figure 1). Although WHR was in the range of 0.58–1.02, there was overlap between men and women only from 0.75 to 0.94. Overall, the 25th percentile among men was approximately equal to the 90th percentile among women (levels of 0.85 and 0.84, respectively), and similar differences were seen within each decade of age (data not shown). Although mean values of Quetelet index also differed ( $p<0.001$ ) between men and women, there was more overlap for this measure; its coefficient of variation was in the range of 13–20%.

### Bivariate Associations

The anthropometric measures were highly interrelated (Table 2). The correlation between waist and hip girths was 0.86, and although Quetelet index was highly correlated with both circumferences, its correlation with WHR was weaker ( $r=0.55$  and  $0.46$ , men and women, respectively). Additionally, age was moderately related to all anthropometric measures ( $r=0.12$ – $0.39$ ). The behavioral characteristics (i.e., cigarette smoking, alcohol consumption, and exercise) were also associated with the anthropometric measures; however, correlations were generally weaker than those shown in Table 2. For example, WHR was inversely related to exercise ( $r=-0.34$  and  $-0.12$ , men and women, respectively), and current smokers had slightly higher levels of WHR than nonsmokers, that is, 0.890 versus 0.876, respectively

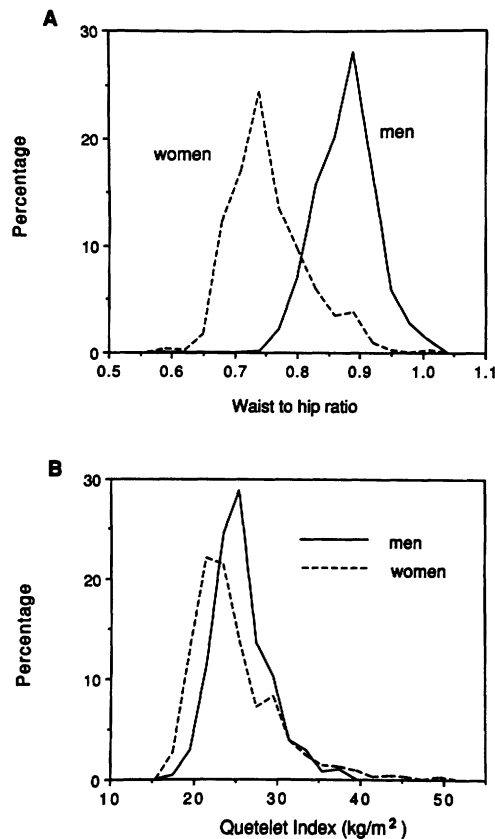


FIGURE 1. Plottings showing comparison of waist-to-hip ratio (WHR) and Quetelet index between men and women. Distinct separation of WHR levels between the two sexes is evident (panel A); however, levels of Quetelet index show much more overlap (panel B).

( $p=0.01$ , men), and 0.760 versus 0.752 ( $p=0.30$ , women) (data not shown). Alcohol consumption was inversely related to Quetelet index among women but not men.

With the exception of HDL cholesterol among men, levels of lipids and lipoproteins were moderately related to age (Table 3). Stronger associations, however, were seen with the anthropometric measures. Correlations with triglycerides tended to be strongest (reaching  $r=0.40$ , with waist girth in women), whereas associations with apolipoprotein A-I were weakest. Because of the strong intercorrelations among the anthropometric measures, however, lipid and lipoprotein levels were related similarly to Quetelet index, waist and hip girths, and WHR. For example, the relation of triglyceride levels to these measures ranged from 0.28 (hip girth) to 0.39 (waist girth) in men. Of the behavioral characteristics, alcohol consumption was positively correlated with levels of HDL cholesterol and apolipoprotein A-I, whereas exercise was inversely related to levels of triglycerides and apolipoprotein B. Furthermore, cigarette smokers tended to have higher levels of triglycerides and apolipoprotein B but lower levels of HDL cholesterol than nonsmokers (data not shown).

#### Sex Differences in Body Fat Distribution and Lipids

To assess the importance of each anthropometric measure in statistically explaining the male/female differences in lipid and lipoprotein levels, several regression models were constructed. Unadjusted male/female differences in lipoprotein levels and the effect of controlling for various characteristics are shown in Table 4. Adjusting for age, alcohol consumption, exercise, and cigarette smoking slightly

TABLE 2. Intercorrelations\* Among the Explanatory Variables

Variable	Sex†	Age	Quetelet index	Waist	Hip	WHR
Age	Men	...	...	...	...	...
	Women	...	...	...	...	...
Quetelet index	Men	0.18‡	...	...	...	...
	Women	0.20‡	...	...	...	...
Waist	Men	0.29‡	0.84‡	...	...	...
	Women	0.25‡	0.89‡	...	...	...
Hip	Men	0.12§	0.81‡	0.86‡	...	...
	Women	0.20‡	0.91‡	0.86‡	...	...
WHR	Men	0.39‡	0.55‡	0.78‡	0.36‡	...
	Women	0.22‡	0.46‡	0.73‡	0.29‡	...

WHR, waist-to-hip ratio.

\*Pearson correlation coefficients; †709 men, 415 women; ‡ $p<0.001$ ; § $p<0.01$ .

TABLE 3. Bivariate Relation\* of the Explanatory Variables to Lipid and Lipoprotein Levels

Variable	Sex	Total cholesterol	Triglycerides†	HDL cholesterol	Total/HDL cholesterol	Apo B	Apo A-I
Age	Men	0.28‡	0.21‡	0	0.17‡	0.24‡	0.11§
	Women	0.47‡	0.29‡	0.16‡	0.22‡	0.38‡	0.24‡
Quetelet index	Men	0.24‡	0.35‡	-0.21‡	0.32‡	0.25‡	-0.12§
	Women	0.15§	0.30‡	-0.20‡	0.29‡	0.23‡	-0.11§
Waist	Men	0.29‡	0.39‡	-0.22‡	0.36‡	0.31‡	-0.16‡
	Women	0.22‡	0.40‡	-0.20‡	0.32‡	0.30‡	-0.08
Hip	Men	0.22‡	0.28‡	-0.15‡	0.26‡	0.21‡	-0.12§
	Women	0.12	0.28‡	-0.17‡	0.23‡	0.18‡	-0.09
WHR	Men	0.27‡	0.37‡	-0.22‡	0.35‡	0.30‡	-0.14‡
	Women	0.26‡	0.38‡	-0.14§	0.30‡	0.34‡	-0.03

HDL, high density lipoprotein; apo B, apolipoprotein B; apo A-I, apolipoprotein A-I; WHR, waist-to-hip ratio.

\*Pearson correlation coefficients, 709 men and 415 women; †values have been log transformed; ‡ $p < 0.001$ ; § $p < 0.01$ .

increased the magnitude of the differences between men and women; and even after controlling for Quetelet index, large contrasts were still evident. (Adjustment for age alone did not alter the unadjusted values.) Controlling for waist girth, however, reduced the male/female differences in levels of triglycerides (from 38 to 10 mg/dl), total/HDL cholesterol (from 1.2 to 0.7), and apolipoprotein B (from 11 to 4 mg/dl); additional decreases were seen with adjustment for hip girth. The effects of adjusting for WHR were comparable to using waist and hip girths separately, with reductions ranging from 21% (apolipoprotein A-I) to 98% (apolipoprotein B).

Stratification was also used to control for differences in levels of WHR between men and women (Table 5). Male/female differences in levels of lipids and lipoproteins were again reduced, with triglycerides, total/HDL cholesterol, and apolipoprotein B showing the largest reductions. For example,

among persons with a WHR of 0.84–0.87, mean triglyceride levels differed by only 1 mg/dl, mean levels of total/HDL cholesterol differed by only 0.2, and mean levels of apolipoprotein B were identical in men and women. Furthermore, these similarities in lipid and lipoprotein levels existed despite large differences in relative weight; as compared with men, mean levels of Quetelet index were 2.4–5.2 kg/m<sup>2</sup> higher among women in the upper three strata of WHR. (Although male/female contrasts in lipid and lipoprotein levels were still seen at WHR levels of less than 0.79, male/female differences in WHR persisted within this group.) The adjusted differences (Table 5, far right column) show the male/female differences in levels of lipids and lipoproteins that would be expected if men and women were similarly distributed across the four WHR groups. (In contrast, 78% of the women were in the lowest WHR group, whereas 51% of the men were in the highest category.)

TABLE 4. Sex Differences in Levels of Lipids and Lipoproteins After Adjustment for Selected Characteristics

Characteristic controlled for	Male excess levels (mg/dl)				
	Triglycerides	HDL cholesterol	Total/HDL cholesterol	Apo B	Apo A-I
None	38‡	-15‡	1.2‡	11‡	-19‡
Covariates*	42‡	-17‡	1.3‡	12‡	-23‡
Covariates plus Quetelet index	37‡	-16‡	1.2‡	11‡	-22‡
Covariates plus waist	10	-12‡	0.7‡	4	-17‡
Covariates plus waist and hip	0	-11‡	0.5‡	1	-16‡
Covariates plus WHR	-2	-10‡	0.4§	0	-15‡
Change in male/female difference† (%)	94	33	66	98	21
Multiple R <sup>2</sup>	0.17	0.28	0.26	0.20	0.24

HDL, high density lipoprotein; apo B, apolipoprotein B; apo A-I, apolipoprotein A-I; WHR, waist-to-hip ratio.

\*Covariates: age, age<sup>2</sup>, alcohol intake, exercise, and current smoking status.

†(Unadjusted difference-adjusted difference)/unadjusted difference. Levels are adjusted for covariates and WHR.

‡ $p < 0.001$ ; § $p < 0.01$ .  $p$  values are for equality of means between men and women.

TABLE 5. Mean Levels of Selected Characteristics Stratified by WHR

	Sex	Levels of WHR				Male/female difference	
		<0.79	0.79–0.83	0.84–0.87	≥0.88	Unadjusted	Adjusted*
<i>n</i>	Men	24	111	209	365	...	...
	Women	322	49	24	20	...	...
Quetelet index (kg/m <sup>2</sup> )	Men	23.5	23.6	24.4	27.3	...	...
	Women	23.6	27.7	29.6	29.7	...	...
WHR	Men	0.78	0.82	0.86	0.92	...	...
	Women	0.73	0.81	0.85	0.90	...	...
Triglycerides (mg/dl)	Men	87±43	81±37	112±85	135±87		
	Women	72±35	97±39	111±70	131±58	38†	–1
HDL cholesterol (mg/dl)	Men	52±11	52±12	49±14	45±12		
	Women	64±16	57±18	54±15	61±16	–15†	–9†
Total/HDL cholesterol	Men	3.8±0.9	3.8±1.1	4.3±1.6	5.0±1.8		
	Women	3.2±1.1	4.1±1.1	4.1±1.1	3.9±1.1	1.2†	0.3
Apo B (mg/dl)	Men	72±20	70±18	78±28	87±23		
	Women	66±19	82±22	78±22	86±27	11†	–3
Apo A-I (mg/dl)	Men	126±18	129±20	125±20	124±21		
	Women	145±28	141±27	136±25	151±28	–19†	–16†

Values are mean±SD.

WHR, waist-to-hip ratio; HDL, high density lipoprotein; apo B, apolipoprotein B; Apo A-I, apolipoprotein A-I.

\*Values have been adjusted for differences in distribution of men and women across four WHR categories.

†*p*<0.001; *p* values are for equality of means between men and women, and were calculated using *F* tests.

Because of the possible effects of sex hormone used on these results, similar analyses were performed within categories of age, using 50 years as a cutoff. Adjusting for WHR reduced the sex differences in levels of the lipids and lipoproteins within each age group. For example, a 15-mg/dl male/female difference in mean levels of HDL cholesterol was reduced to 9 mg/dl among the 921 younger subjects; among the 202 persons more than 50 years old, the differential was reduced from 14 to 5 mg/dl.

Men and women were then matched on WHR (to the nearest 0.01), resulting in 118 pairs with a mean WHR of 0.83. Despite women being more overweight (+3.5 kg/m<sup>2</sup>) than men in these matched pairs, male/female differences were reduced for levels of triglycerides (to 4 mg/dl), HDL cholesterol (to 7 mg/dl), total/HDL cholesterol (to 0.6), and apolipoprotein A-I/HDL cholesterol (to 0.01).

### Discussion

Although it is uncertain why men in industrialized societies have higher rates of coronary heart disease than women, differences in levels of HDL cholesterol might account for much of the contrast.<sup>9</sup> The present results indicate that body fat distribution (or a highly correlated characteristic) can be an important determinant of male/female differences in levels of triglycerides, HDL cholesterol, total/HDL cholesterol, and apolipoproteins A-I and B. In this study of 1,124 employed adults, men had higher levels of triglycer-

ides and apolipoprotein B together with lower levels of HDL cholesterol and apolipoprotein A-I. Controlling for WHR in several types of analyses greatly reduced these sex differences in levels of lipids and lipoproteins. For example, the male excess in levels of triglycerides was reduced by 97% with stratification, by 94% with analysis of covariance, and by 89% with a matched-pairs analysis.

Many of the detrimental effects of obesity depend on the anatomic localization of adipose tissue, with a relative excess of body fat on the trunk and upper body associated with adverse levels of lipoproteins,<sup>15,16</sup> diabetes mellitus,<sup>13</sup> and coronary heart disease.<sup>17,18</sup> Although both Quetelet index and WHR are related to levels of lipids and lipoproteins, the relative importance of body fat distribution in explaining the male/female differences in the present study was remarkable. For example, controlling for WHR reduced the sex differences in levels of apolipoprotein B and triglycerides by more than 90%, but adjustment for Quetelet index had no effect. Furthermore, at comparable levels of WHR, men and women had similar levels of lipids and lipoproteins despite large differences in Quetelet index. In agreement with these results, Foster et al<sup>27</sup> reported that body fatness (as measured by tritium dilution) was not related to lipoprotein levels in either sex after controlling for fat patterning and body build.

WHR is a relatively simple index of upper-body and abdominal obesity.<sup>28</sup> Although waist girth and

WHR showed comparable associations with levels of lipids and lipoproteins in the present study, WHR is less strongly related to Quetelet index and is highly correlated with the proportion of visceral fat.<sup>29</sup> Furthermore, WHR might be a better predictor of subsequent cardiovascular disease than is waist circumference.<sup>29</sup> Although more accurate measurement of fat distribution (such as a series of skinfold or circumference measurements or computed tomography) might be more predictive of metabolic and clinical complications,<sup>29-31</sup> WHR has been consistently related to adverse levels of triglycerides and HDL cholesterol.<sup>14-16,28,31</sup> In contrast, levels of total cholesterol are less strongly associated with body fat distribution,<sup>30,32</sup> and mean levels did not differ between men and women. The relation of behavioral characteristics to body fat distribution has been previously examined, and in agreement with the present results, higher levels of WHR have been found among cigarette smokers.<sup>33-35</sup>

There are several mechanisms whereby deposition of adipose tissue in the abdominal region could result in metabolic disturbances.<sup>14,28</sup> Even after considering relative weight, decreases in skeletal muscle sensitivity to insulin and hepatic removal of insulin are seen in women with abdominal obesity.<sup>36</sup> Furthermore, abdominal fat cells are characterized by relatively high rates of lipolysis.<sup>15</sup> Because free fatty acids from intra-abdominal adipocytes can drain directly into the portal circulation, the amount of visceral fat (which is highly correlated with WHR<sup>29,31</sup>) might be the most important aspect of body fat topography.

It is possible, however, that levels of estrogen and androgens mediate the association between fat patterning and lipoproteins. Sexual maturation in the female rat is associated with preservation of undifferentiated preadipocytes only in the femoral region.<sup>37</sup> During adolescence, boys deposit more fat in truncal areas than girls<sup>38</sup> and undergo a decrease in levels of HDL cholesterol.<sup>39</sup> Furthermore, levels of free testosterone in nonhirsute women are related to WHR<sup>40</sup> and impaired peripheral insulin sensitivity.<sup>41</sup>

Decreased levels of sex hormone-binding globulin, reflecting a relative excess of unbound androgen to estrogen, have also been related to WHR in men<sup>40,42</sup> and women<sup>43,44</sup> and to adverse levels of lipids and lipoproteins.<sup>43</sup> Although few studies have included measurements of body fat distribution, sex hormones, and levels of lipoproteins, Stefanick et al<sup>42</sup> found that controlling for WHR reduced the relation of sex hormone-binding globulin to levels of triglycerides and HDL<sub>2</sub> cholesterol. It is possible that the relation of fat patterning to lipoprotein levels might be partly due to their joint association with sex hormones. Insulin resistance in hyperandrogenized, nonobese women can be partially overcome by the administration of an antiandrogen.<sup>11</sup>

Despite the pronounced reduction in male/female differences in lipoprotein levels seen in the present study, several limitations of its design should be considered. Subjects were employed volunteers, and

approximately 50% of eligible persons participated. Although this rate is lower than those seen in community-based studies,<sup>45</sup> it is comparable to other studies of employed populations.<sup>46</sup> Persons with a history of hyperlipidemia might have been more likely to have volunteered,<sup>47</sup> and a selection bias would have resulted if participation of these persons were related to body fat distribution.<sup>48</sup> Levels of several characteristics, however, were comparable with those reported by other investigators. For example, 25-34-year-old men in the present study ( $n=249$ ) had mean levels of 25.1 kg/m<sup>2</sup> (Quetelet index), 191 mg/dl (total cholesterol), and 48 mg/dl (HDL cholesterol) as compared with levels of 25.2 kg/m<sup>2</sup>, 188 mg/dl, and 45 mg/dl, respectively, reported by the National Health Survey<sup>49</sup> and the Lipid Research Clinics Prevalence Study.<sup>50</sup> Among similarly aged women ( $n=152$ ), corresponding levels were 23.6 kg/m<sup>2</sup>, 185 mg/dl, and 61 mg/dl in the present study versus 23.8 kg/m<sup>2</sup>, 174 mg/dl, and 56 mg/dl. Furthermore, the observed associations between Quetelet index, cigarette smoking, alcohol consumption, and exercise with lipid and lipoprotein levels were comparable with those reported by others.<sup>51</sup> Because of these similarities, it is unlikely that a selection bias substantially influenced the results.

The relatively slight overlap of WHR between men and women might be due to the inclusion of employed volunteers, and additional studies are needed to extend the current findings to persons with extreme levels of WHR. Furthermore, although 74 women were more than 50 years old, no information was collected on the use of postmenopausal hormones, which can affect levels of lipids and lipoproteins.<sup>3,4</sup> (Based on other studies in Milwaukee,<sup>52</sup> about 15% of these older women might have been using estrogens.) Stratified analyses, however, showed that adjustment for WHR reduced the male/female differences in lipoproteins among younger and older participants. Although it is also possible that WHR was misclassified, this would have resulted in the persistence of male/female differences in lipoprotein levels after controlling for body fat distribution.

Because of the cross-sectional study design, the temporal relation of body fat distribution to lipoprotein levels is unclear. However, the large proportion of differences in lipoprotein levels between men and women that can be attributed to body fat distribution as well as the plausible biological mechanisms suggest that body fat distribution (or a highly related characteristic) is an important determinant of differences in lipid and lipoprotein levels between men and women.

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