Sex Differences and Coronary Heart Disease
A Case of Comparing Apples and Pears?

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Vital statistics and prospective population-based studies in Rancho Bernardo, Framingham, and Alameda County demonstrate that men have higher rates of morbidity and mortality from coronary heart disease (CHD) than do women. Numerous studies also indicate that there are substantial gender differences in lipoprotein levels; men have higher levels of triglycerides and low density lipoprotein (LDL) cholesterol (associated with higher CHD risk), whereas women have higher levels of high density lipoprotein (HDL) cholesterol (associated with lower risk). Prospective studies have also demonstrated that lipid levels are significant risk factors for CHD among both men and women, although they do not entirely explain the gender difference in CHD risk.

More controversial is the association between obesity and CHD, where associations are inconsistent in strength and pattern and often apply to only one sex or the other. Stern and Haffner propose that some of this inconsistency may reflect differences in which covariates were included in multivariate models for each study. For example, obesity may predispose individuals to hypertension and abnormal lipid levels. If each of these variables is included in a multivariate model, obesity may become statistically nonsignificant while still being biologically meaningful.

Björntorp proposes that the inconsistencies in the literature on obesity and CHD risk may occur because only subgroups of persons with obesity are at increased risk, and the populations examined had different proportions of high-risk subgroups.

Fat distribution, one mechanism for identifying adiposity subgroups, also focuses on gender differences in obesity patterns. As Vague noted in 1956, upper body ("android") obesity is more common among men, whereas lower body ("gynoid") obesity is more common among women. In addition, he noted that upper body obesity was strongly associated with atherosclerosis, diabetes, and gout, whereas lower body obesity was not.

Upper/lower body obesity has also been referred to as central/peripheral obesity, abdominal/extremity adiposity, visceral/gluteofemoral fat distribution, and "apple" versus "pear" shape. Hartz and colleagues introduced the ratio of waist-to-hip circumferences as a convenient index for measuring these differences. Computed tomography demonstrates that high waist-to-hip ratios (WHRs) are associated with high levels of intraabdominal or visceral fat but not subcutaneous fat.

In an article in this issue of Circulation, Freedman and colleagues refocus attention on gender differences in CHD risk by focusing on gender differences in WHRs. In an illuminating graphic representation, they demonstrate that WHR differentiates obesity patterns by sex much better than does body mass index (BMI). Using a sample of 1,124 employed men and women, they also demonstrate that adjustment for WHR by analysis of covariance, stratification, or matching greatly reduced gender differences in lipoprotein levels, whereas adjustment for BMI did not. These cross-sectional analyses were adjusted for differences in alcohol intake, exercise, and current smoking status, behaviors that vary by sex and are known to influence lipid levels.

Peiris and colleagues have also demonstrated that visceral fat, as measured by WHR and computed tomography, was more strongly associated with lipid levels than was total body fat as measured by hydrostatic weighing.

Numerous other cross-sectional studies, especially in the past 2 years, have also demonstrated that body fat distribution is associated with lipid levels. In healthy men and women in obese premenopausal and postmenopausal women, and in obese men, high WHRs were associated with decreased HDL cholesterol levels (especially HDL2) and increased total cholesterol, LDL cholesterol, and triglyceride levels. Most of these studies found the effect to be independent of BMI, although Landin and colleagues found the association mainly among the obese.

Peiris and colleagues found that 60% of the variance in triglyceride levels and 15% of the variance in the ratio of HDL cholesterol to total cholesterol were explained by differences in visceral fat mass, whereas Ostlund and colleagues found that 32% of the variance of HDL cholesterol levels...
was explained by variations in WHR. Focusing on
gender differences, Freedman and colleagues15
found that WHR explained 94% of the sex difference
in triglyceride levels, 33% of sex differences in HDL
cholesterol levels, and 66% of the ratio of total
cholesterol to HDL cholesterol levels. Although
none of the other cross-sectional studies evaluated
the contribution of WHR to gender differences in
lipid levels in this way, Ostlund and colleagues21
did find that sex was no longer a significant predictor of
HDL cholesterol levels after adjustment for WHR,
BMI, plasma glucose, insulin, and diet.

At least three prospective studies have demon-
strated that body fat distribution is associated with
subsequent CHD, even after adjustment for differ-
ences in BMI.22–24 Among 792 men in Gothenburg,
Sweden, who were followed up for 13 years, WHR
was more strongly associated with stroke, ischemic
heart disease, and death than was BMI, although the
association was not independent of cigarette smok-
ing, blood pressure, or cholesterol levels.22 Among
1,462 women also from Gothenburg, Sweden, fol-
lowed up for 12 years, the association with WHR was
independent of these risk factors.23 Finally, using
trunk-to-thigh skinfold measurements, an indepen-
dent association of body fat distribution to incident
CHD was demonstrated among 7,746 men in Paris,
France, followed up for 6.6 years.24 In addition, two
prospective studies, the Honolulu Heart Study25 of
7,692 Japanese men followed up for 12 years and the
Framingham Heart Study26 of men and women fol-
lowed up for 22 years, have demonstrated an associ-
ation between subscapular skinfold measurements
(upper body fat) and incident CHD, independent of
BMI and other CHD risk factors. Neither of the
latter studies evaluated an upper-to-lower body fat
ratio.

The only prospective study of body fat distribution
and CHD to include both men and women, the
Framingham Study,26 found upper body fat was more
strongly associated with incident CHD in men than in
women, whereas the two studies from Sweden22,23
indicated that WHR was more strongly associated
with heart disease risk in women than in men (risk
ratios for highest to lowest WHR quintile of 8.2 for
myocardial infarction in women and 2.5 for ischemic
heart disease in men). After adjustment for choles-
terol levels and blood pressure, this association was
significant only in women. However, these risk fac-
tors may be part of the mechanism whereby WHR
influences heart disease risk.

In addition to cholesterol levels, plasma insulin,
glucose, and hormone levels have been suggested as
mechanisms whereby WHR influences CHD risk.8
Numerous studies have shown that WHR is associ-
ated with these other CHD risk factors. However,
several recent cross-sectional studies indicate that
WHR remains significantly associated with lipid lev-
els after adjustment for hormone levels,18 insulin
levels,14,21 blood pressure,14,16 and BMI,16–19,21 sug-
gesting that some other factors associated with WHR
are also involved in the association of body fat
distribution and lipid levels.

In summary, men have higher CHD morbidity and
mortality rates than women1–4 and different lipoprotein
patterns.5,6 WHR predicts lipoprotein levels14,16–21
and CHD rates22–26 in both men and women and may
help explain gender differences in lipoprotein
levels15,20 as well as CHD risk. Further prospective
analyses are needed in populations that include both
men and women, that focus on the gender differen-
tial in CHD risk, and that include measures of lipids,
inulin, glucose tolerance, and other CHD risk factors,
including body fat distribution. Given the high corre-
lation of WHR and gender, it is possible that fat
distribution and its associated metabolic changes
explain many of the sex differentials in CHD. Perhaps
we should be counting “apples” and “pears,” not men
and women. Alternatively, we may find that fat distrib-
ution and other aspects of gender influence health.
By understanding these gender differences in CHD
risk, we may be better able to counsel all individuals
on how to reduce their risk.

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