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 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 HDL_2) 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 colleagues\textsuperscript{15} 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 colleagues\textsuperscript{21} 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 demonstrated that body fat distribution is associated with subsequent CHD, even after adjustment for differences in BMI.\textsuperscript{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 smoking, blood pressure, or cholesterol levels.\textsuperscript{22} Among 1,462 women also from Gothenburg, Sweden, followed up for 12 years, the association with WHR was independent of these risk factors.\textsuperscript{23} Finally, using trunk-to-thigh skinfold measurements, an independent association of body fat distribution to incident CHD was demonstrated among 7,746 men in Paris, France, followed up for 6.6 years.\textsuperscript{24} In addition, two prospective studies, the Honolulu Heart Study\textsuperscript{25} of 7,692 Japanese men followed up for 12 years and the Framingham Heart Study\textsuperscript{26} of men and women followed up for 22 years, have demonstrated an association 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,\textsuperscript{26} found upper body fat was more strongly associated with incident CHD in men than in women, whereas the two studies from Sweden\textsuperscript{22,23} 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 cholesterol levels and blood pressure, this association was significant only in women. However, these risk factors 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.\textsuperscript{8} Numerous studies have shown that WHR is associated with these other CHD risk factors. However, several recent cross-sectional studies indicate that WHR remains significantly associated with lipid levels after adjustment for hormone levels,\textsuperscript{18} insulin levels,\textsuperscript{14,21} blood pressure,\textsuperscript{14,16} and BMI,\textsuperscript{16–19,21} suggesting 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 women\textsuperscript{1–4} and different lipoprotein patterns.\textsuperscript{5,6} WHR predicts lipoprotein levels\textsuperscript{14,16–21} and CHD rates\textsuperscript{22–26} in both men and women and may help explain gender differences in lipoprotein levels\textsuperscript{15,20} as well as CHD risk. Further prospective analyses are needed in populations that include both men and women, that focus on the gender differential in CHD risk, and that include measures of lipids, insulin, glucose tolerance, and other CHD risk factors, including body fat distribution. Given the high correlation 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 distribution 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.

References


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