Relationship of Physical Fitness vs Body Mass Index With Coronary Artery Disease and Cardiovascular Events in Women

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Obesity is increasingly recognized as a public health epidemic and modifiable risk factor for coronary heart disease (CHD).1,2 Among adult US women and men, nearly two thirds are overweight and more than one third are obese, and these proportions are rapidly increasing.1,3 Numerous studies have shown that anthropometric indices including body mass index (BMI), waist circumference, waist-hip ratio, and waist-height ratio are associated with CHD risk factors or adverse events.4-9 Previous reports have documented that increased cardiovascular (CV) risk associated with being overweight is partially explained by its association with numerous risk mediators, including traditional atherosclerotic risk factors, insulin resistance, inflammation, and endothelial dysfunction.5-7,10

Context Individual contributions of obesity and physical fitness (physical activity and functional capacity) to risk of coronary heart disease in women remain unclear.

Objective To investigate the relationships of measures of obesity (body mass index [BMI], waist circumference, waist-hip ratio, and waist-height ratio) and physical fitness (self-reported Duke Activity Status Index [DASI] and Postmenopausal Estrogen-Progestin Intervention questionnaire [PEPI-Q] scores) with coronary artery disease (CAD) risk factors, angiographic CAD, and adverse cardiovascular (CV) events in women evaluated for suspected myocardial ischemia.

Design, Setting, and Participants The National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE) is a multicenter prospective cohort study. From 1996-2000, 936 women were enrolled at 4 US academic medical centers at the time of clinically indicated coronary angiography and then assessed (mean follow-up, 3.9 [SD, 1.8] years) for adverse outcomes.

Main Outcome Measures Prevalence of obstructive CAD (any angiographic stenosis ≥50%) and incidence of adverse CV events (all-cause death or hospitalization for nonfatal myocardial infarction, stroke, congestive heart failure, unstable angina, or other vascular events) during follow-up.

Results Of 906 women (mean age, 58 [SD, 12] years) with complete data, 19% were of nonwhite race, 76% were overweight (BMI ≥25), 70% had low functional capacity (DASI scores ≤25, equivalent to ≤7 metabolic equivalents [METs]), and 39% had obstructive CAD. During follow-up, 337 (38%) women had a first adverse event, 118 (13%) had a major adverse event, and 68 (8%) died. Overweight women were more likely than normal weight women to have CAD risk factors, but neither BMI nor abdominal obesity measures were significantly associated with obstructive CAD or adverse CV events after adjusting for other risk factors (P=.05 to .88). Conversely, women with lower DASI scores were significantly more likely to have CAD risk factors, but neither BMI nor abdominal obesity measures were significantly associated with obstructive CAD or adverse CV events after adjusting for other risk factors (P=.05 to .88). Conversely, women with lower DASI scores were significantly more likely to have CAD risk factors and obstructive CAD (44% vs 26%, P<.001 at baseline, and each 1-MET increase in DASI score was independently associated with an 8% (hazard ratio, 0.92; 95% confidence interval, 0.85-0.99; P=.02) decrease in risk of major adverse CV events during follow-up.

Conclusions Among women undergoing coronary angiography for suspected ischemia, higher self-reported physical fitness scores were independently associated with fewer CAD risk factors, less angiographic CAD, and lower risk for adverse CV events. Measures of obesity were not independently associated with these outcomes.

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See also pp 1188 and 1232.
activity and functional capacity, which are also known to predict risk for CHD.5,11-13 Some studies show physical activity and fitness to be predictive of CV risk incrementally and independently of anthropometric indices and traditional CV risk factors.14-18 Moreover, many studies of physical activity and fitness have excluded women with known or suspected CHD.7,16,19-21 Roles of obesity and fitness as independent risk factors for CHD and adverse events in women remain unresolved. Therefore, we investigated the relationships of physical fitness and obesity measures with CHD risk factors, coronary angiographic findings, and adverse events among a group of women undergoing coronary angiography to evaluate suspected ischemia.

**METHODS**

**Study**

The Women’s Ischemia Syndrome Evaluation (WISE) is a multicenter study sponsored by the National Heart, Lung, and Blood Institute and designed to improve diagnostic testing for coronary artery disease (CAD) in women. Details of the WISE design and methods have been published.22 Briefly, between 1996 and 2000, 936 women with chest discomfort, suspected myocardial ischemia, or both were enrolled at the time of referral for clinically indicated coronary angiography. Each WISE site obtained consent for patient testing through its institutional review board. Each woman provided written informed consent to have the testing performed and to be contacted during follow-up.

Baseline evaluation included collection of demographic, symptom, cardiac risk factor, medical history, physical activity, physical examination, and laboratory data. Participants classified their race/ethnicity during completion of the baseline form with the nurse coordinator or physician using US Census Bureau standard categories. Race/ethnicity was assessed to investigate racial differences in women with CAD and to allow this variable to be controlled for in future analyses if informative. Some of the women underwent additional diagnostic testing, such as exercise treadmill testing and coronary vasoreactivity testing, based on the site of enrollment as previously described.22 Quantitative and qualitative analyses of CAD were performed by the WISE angiographic core laboratory.23 Blood lipid and inflammatory marker levels were quantified by WISE core laboratories.24,25

**Obesity Assessment**

Body mass index was defined as weight in kilograms divided by the square of height in meters, with normal weight defined as BMI less than 25, overweight as BMI 25 through 29, and obese as BMI 30 or greater. Waist circumference was measured at the umbilicus, with normal defined as 88 cm or less.3 Waist-hip ratio was calculated as 100 × (maximal waist circumference in centimeters/maximal hip circumference in centimeters), with normal defined as less than 80.26 Waist-height ratio was calculated as maximal waist circumference in centimeters/height in meters, with normal defined as less than 50.20

**Fitness Assessment**

To evaluate physical fitness, we used the Duke Activity Status Index (DASI) questionnaire, an assessment of functional capacity derived from self-reported ability to perform various activities that correlates with exercise treadmill results.27 Positive response scores are summed to get a total score that is an estimate of maximal oxygen consumption, which ranges from 0 to 52.2 mL/kg per minute. This total score can be divided by 3.5 to estimate metabolic equivalent tasks (METs). A score of at least 25 (≥7 METs) was defined as normal. This level approximates completion of the second stage of a Bruce treadmill protocol (roughly equivalent to being able to walk at 5 mph, jog, or participate in many non-contact sports) and was significantly related to lower rates of CAD and risk factors in previous WISE analyses.18

To evaluate physical activity, a contributor to fitness, we used the Postmenopausal Estrogen-Progestin Intervention questionnaire (PEPI-Q), a self-reported estimate of average physical activity level at home, work, and leisure.28 If question 1 regarding activity at work was answered “not applicable,” the PEPI-Q was adjusted by using the average of the other 2 answers as the third value. No validated threshold for PEPI-Q categories is available, so PEPI-Q was used as a continuous variable.

Scores for both the DASI and the PEPI-Q have been correlated with treadmill functional capacity measured in METs (r = 0.31, P < .001 and r = 0.27, P = .01, respectively) and validated within a representative subset of the WISE cohort.18

**Follow-up**

Follow-up data were collected in person or by telephone interview by an experienced nurse, physician, or both at 6 weeks after enrollment and then yearly. Participants were queried for occurrence of adverse events, and referring physicians were contacted for confirmation, dates, and documentation when an adverse event was identified. In the event of death, a death certificate was obtained.

**Definitions**

Angiographically determined obstructive CAD was protocol-specified as any luminal diameter stenosis of 50% or greater; severe CAD was defined as any luminal diameter stenosis of 70% or greater. A prospectively developed WISE CAD severity score has been described in detail22 and was assigned based on angiographic severity of stenoses, location of stenoses, and presence of partial or complete collateral flow, with a range of 5.0 to 88.5. The metabolic syndrome was defined by Adult Treatment Panel III criteria as participants’ having at least 3 of the following: (1) waist circumference of 88 cm or greater or BMI of 30 or greater; (2) systolic blood pressure of 130 mm Hg or greater and diastolic blood pressure of 85 mm Hg or greater; (3) triglyceride level of 150 mg/dL or greater; (4) fasting blood
Prior CAD was defined as history of myocardial infarction (MI), percutaneous coronary intervention, or coronary artery bypass graft surgery. All adverse events were defined as all-cause death or hospitalization for nonfatal MI, stroke, congestive heart failure, unstable angina, or other vascular events. Major adverse events were defined as death, nonfatal MI, or nonfatal stroke. Myocardial infarction was defined by elevation of creatine kinase-MB isoenzyme level at least 5 times the upper limit of the reference range. Other vascular events included primarily peripheral arterial or venous events, such as carotid endarterectomy or deep venous thrombosis.

### Statistical Methods
Data are summarized as mean (SD) or percentages as indicated. To ascertain trends in baseline characteristics across categories of BMI (Table 1), the following factors were considered: BMI, age, waist circumference, waist-to-hip ratio, waist-to-height ratio, diastolic blood pressure, total cholesterol, HDL cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, and fasting glucose. The chi-square test was used to analyze qualitative variables and the Student’s t-test to compare quantitative variables between the two groups. A p-value of less than 0.05 was considered statistically significant.
we used Mantel-Haenszel tests for frequencies; for continuous data we used Jonkheere-Terpstra tests (a nonparametric method to detect ordered differences in distributions of continuous variables across ordered groups). We also compared the same characteristics for DASI categories (Table 1) using logistic regression analysis, with P values adjusted for age. Adverse events were evaluated as all adverse events and as major adverse events. We used χ² analysis to evaluate the incidence of events across the 4 categories of obesity/fitness and Kaplan-Meier plots to evaluate event-free survival during follow-up.

Standard multivariate logistic regression techniques were used to assess obstructive CAD, and multivariate Cox regression models were used to assess adverse events. We performed multivariate modeling in 2 steps. The first was to develop a basic risk model for each outcome using forward stepwise logistic or Cox regression techniques. Characteristics in Table 1, except fitness or obesity variables, with P values less than .10 for univariable associations with obstructive CAD or adverse events were considered for inclusion in each model. Notably, both obstructive CAD (ie, any angiographic stenosis ≥50%) and WISE CAD severity score were assessed for multivariate relationships with adverse events. Significant predictors that remained in each model are listed in the appropriate paragraph in the “Results” section and in the footnote to each multivariate model table.

The second step of multivariate modeling was to separately add DASI scores, PEPI-Q scores, and the obesity variables to this basic risk model. Because of strong correlations among the fitness and obesity variables, their predictive ability was evaluated in separate models, each time adjusting for the same set of significant covariates. The final models were evaluated for other linear relationships among variables in the model (collinearity), which have the potential of rendering significance testing unreliable. Using standard diagnostic techniques, all models presented were found to be free from collinearity (tolerance, 0.64-0.97). All tests were 2-sided, and significance testing unreliable. Using standard diagnostic techniques, all models presented were found to be free from collinearity (tolerance, 0.64-0.97). All tests were 2-sided, and a P value less than .05 was considered statistically significant. Data were analyzed using SAS version 8.2 (SAS Institute Inc, Cary, NC).

### RESULTS

#### Study Population

Among 906 women (mean age, 58 [SD, 12] years) with complete data, 19% were nonwhite, 24% had a history of diabetes mellitus, 59% of hypertension, 55% of dyslipidemia, 20% currently smoked, and 53% had a history of smoking. Angiographically, 349 (39%) of the women had obstructive CAD (50% luminal diameter stenosis), including 216 (24%) with severe CAD (≥70% luminal diameter stenosis).

#### Body Mass Index

Of the 906 women, 693 (76%) were overweight (BMI ≥25), and 374 (41%) were obese (BMI ≥30). When analyzed by categories of BMI (Table 1), higher BMI was significantly associated with nonwhite race and higher prevalence of hypertension, diabetes, and dyslipidemia. Higher BMI was also associated with lower average age, less current smoking, higher systolic and diastolic blood pressure, lower levels of high-density lipoprotein cholesterol, higher levels of fasting blood glucose and triglycerides, higher levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6), and higher prevalence of the metabolic syndrome. Body mass index strongly correlated with other anthropometric indices. Higher BMI was associated with lower DASI and PEPI-Q scores. However, despite this preponderance of CAD risk factors associated with higher BMI, there was no difference in presence or severity of angiographic CAD among the BMI categories (Table 1).

#### Fitness

When categorized by DASI score less than 25 (approximately 7 METs), 631 women (70%) had low functional capacity (Table 1). Women with low functional capacity were older and less likely to be white or using hormone therapy. Women with low functional capacity were more likely to have a history of hypertension, diabetes, dyslipidemia, menopause, or smoking. They had significantly higher mean anthropometric measurements, systolic blood pressures, triglyceride levels, IL-6 levels, and prevalence of the metabolic syndrome. Furthermore, women with lower DASI scores had significantly higher WISE CAD severity scores and were significantly more likely to have both obstructive and severe angiographic CAD (Table 1).

Both DASI and PEPI-Q scores were significantly lower for women with the metabolic syndrome or diabetes across all categories of BMI (data not shown), suggesting that women with these dysmetabolic conditions were significantly less active or had lower functional capacities than women with normal metabolic status, regardless of weight. Additionally, DASI score as a continuous variable was inversely correlated with blood levels of hs-CRP (r = −0.19, P < .001), IL-6 (r = −0.14, P < .001), and serum amyloid A (r = −0.10, P = .01). Furthermore, women with a history of ever smoking had significantly lower mean (SD) DASI scores (18.7 [14.8] vs 21.4 [14.6],
FITNESS VS OBESITY AND CARDIOVASCULAR EVENTS

P = .007) and PEPI-Q scores (7.1 [2.0] vs 7.5 [2.0], P = .001) than women with no history of smoking.

Angiographic CAD

Table 2 summarizes the independent predictive ability of anthropometric measures as well as DASI and PEPI-Q scores in separate models adjusted for other significant predictors of CAD in the WISE cohort (age, diabetes, dyslipidemia, use of hormone therapy, pulse pressure, hs-CRP level, triglyceride level, fasting blood glucose level, and aspirin use). We found no significant relationships between the proportion of women with obstructive CAD and any categorical (data not shown) or continuous anthropometric measurement (Table 2), except for a trend toward lower likelihood of obstructive CAD with increasing BMI (P = .05). In contrast, even after adjusting for other significant predictors of CAD, we found significant associations between risk of obstructive CAD and PEPI-Q score (Table 2) as well as both continuous (Table 2) and categorical DASI score: a DASI score less than 25 was associated with more than a 2-fold risk of having obstructive CAD (hazard ratio [HR], 2.21; 95% confidence interval [CI], 1.62-3.01; P = .01).

Adverse Events

Complete follow-up data were available for 880 (97%) of the 906 women. Overall, after a mean follow-up time of 3.9 (SD, 1.8) years, 337 (38%) of the women had experienced a first adverse event, 118 (13%) a major adverse event, and 68 (8%) had died. Table 3 summarizes the adverse events and their associations with categories of BMI or DASI scores. Table 4 summarizes the univariate associations of measures of obesity and fitness with all adverse events, major adverse events, and all-cause mortality.

Categorically or continuously, BMI was not associated with risk of all adverse events, major adverse events, or all-cause mortality (P > .10 for all) in univariate analyses. In contrast, risks of all adverse events and major adverse events were associated with categorical (P < .05 for all, data not shown) and continuous waist circumference, waist-hip ratio, and weight-height ratio, before adjusting for other predictors (Table 4). No anthropometric measurement was associated with all-cause mortality (P ≥ .10 for all). Furthermore, after adjusting for significant risk factors for all adverse events (race; history of dyslipidemia, diabetes, or smoking; prior CAD; diastolic blood pressure; and WISE CAD severity score) or major adverse events (history of diabetes or smoking, prior CAD,

Table 3. Women With Adverse Events, by BMI or DASI Category

<table>
<thead>
<tr>
<th>Event*</th>
<th>Overall, No. (%)</th>
<th>Normal (n = 210)</th>
<th>Overweight (n = 312)</th>
<th>Obese (n = 358)</th>
<th>P Value*</th>
<th>Low (n = 610)</th>
<th>High (n = 270)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>68 (8)</td>
<td>21 (10)</td>
<td>20 (6)</td>
<td>27 (8)</td>
<td>.38</td>
<td>55 (9)</td>
<td>13 (5)</td>
<td>.06</td>
</tr>
<tr>
<td>MI</td>
<td>28 (3)</td>
<td>6 (3)</td>
<td>7 (2)</td>
<td>15 (4)</td>
<td>.29</td>
<td>23 (4)</td>
<td>5 (2)</td>
<td>.13</td>
</tr>
<tr>
<td>Death or MI</td>
<td>91 (10)</td>
<td>26 (12)</td>
<td>25 (8)</td>
<td>40 (11)</td>
<td>.76</td>
<td>74 (12)</td>
<td>17 (6)</td>
<td>.02</td>
</tr>
<tr>
<td>CHF</td>
<td>50 (6)</td>
<td>14 (7)</td>
<td>13 (4)</td>
<td>23 (6)</td>
<td>.91</td>
<td>46 (8)</td>
<td>4 (1)</td>
<td>.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>34 (4)</td>
<td>4 (2)</td>
<td>16 (5)</td>
<td>14 (4)</td>
<td>.34</td>
<td>30 (5)</td>
<td>4 (1)</td>
<td>.02</td>
</tr>
<tr>
<td>Angina</td>
<td>230 (26)</td>
<td>51 (24)</td>
<td>73 (23)</td>
<td>106 (30)</td>
<td>.11</td>
<td>179 (29)</td>
<td>51 (19)</td>
<td>.001</td>
</tr>
<tr>
<td>Other vascular events</td>
<td>60 (7)</td>
<td>10 (5)</td>
<td>25 (8)</td>
<td>25 (7)</td>
<td>.40</td>
<td>50 (8)</td>
<td>10 (4)</td>
<td>.02</td>
</tr>
<tr>
<td>Major events</td>
<td>118 (13)</td>
<td>29 (14)</td>
<td>40 (12)</td>
<td>49 (13)</td>
<td>.90</td>
<td>99 (16)</td>
<td>19 (7)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>All events</td>
<td>337 (38)</td>
<td>76 (36)</td>
<td>118 (38)</td>
<td>143 (40)</td>
<td>.36</td>
<td>267 (44)</td>
<td>70 (26)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CHF, congestive heart failure; DASI, Duke Activity Status Index; MI, myocardial infarction.
*MI defined as fatal or nonfatal MI; CHF, as hospitalization for CHF; stroke, as fatal or nonfatal stroke; other vascular events as hospitalization for other vascular events (primarily peripheral arterial or venous disorders); angina, as hospitalization for angina; major events as all-cause death, nonfatal MI, or nonfatal stroke; and all events, as all-cause death or hospitalization for nonfatal MI, nonfatal stroke, CHF, unstable angina, or other vascular events.

Table 4. Univariate Relationships Between Risk of Adverse Events and Continuous Variables

<table>
<thead>
<tr>
<th>Variable*</th>
<th>All Adverse Events</th>
<th>Major Adverse Events</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)†</td>
<td>P Value</td>
<td>HR (95% CI)†</td>
</tr>
<tr>
<td>BMI</td>
<td>1.01 (0.99-1.02)</td>
<td>.37</td>
<td>1.00 (0.97-1.02)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.02 (1.01-1.04)</td>
<td>.009</td>
<td>1.02 (1.00-1.05)</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>1.02 (1.01-1.03)</td>
<td>.002</td>
<td>1.01 (1.00-1.03)</td>
</tr>
<tr>
<td>Waist-height ratio</td>
<td>1.01 (1.00-1.02)</td>
<td>.01</td>
<td>1.02 (1.00-1.03)</td>
</tr>
<tr>
<td>PEPI-Q</td>
<td>0.88 (0.83-0.92)</td>
<td>&lt; .001</td>
<td>0.79 (0.72-0.86)</td>
</tr>
<tr>
<td>DASI METs</td>
<td>0.90 (0.88-0.93)</td>
<td>&lt; .001</td>
<td>0.96 (0.94-0.98)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; DASI METs, Duke Activity Status Index metabolic equivalent tasks; HR, hazard ratio; PEPI-Q, Postmenopausal Estrogen-Progestin Intervention Study questionnaire.
*See “Methods” section for definitions.
P/Per whole unit of measurement for each variable.
hs-CRP level, hemoglobin level, and WISE CAD severity score), no significant relationships were found between anthropometric measures and all adverse events or major adverse events (FIGURE 1).

**FIGURE 1.** Adjusted Risk of All Adverse Events and Major Adverse Events, by Continuous Variables Evaluated in Separate Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Adjusted Risk of All Adverse Events</th>
<th>Adjusted Risk of Major Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.01 (0.99-1.02)</td>
<td>.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist Circumference</td>
<td>1.01 (0.99-1.03)</td>
<td>.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist-Hip Ratio</td>
<td>1.01 (0.99-1.02)</td>
<td>.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist-Height Ratio</td>
<td>1.01 (0.99-1.02)</td>
<td>.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEPI-Q</td>
<td>0.93 (0.88-0.99)</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DASI METs</td>
<td>0.93 (0.90-0.96)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios are per whole unit of measurement for each variable. All adverse events were defined as all-cause death or hospitalization for nonfatal myocardial infarction, stroke, congestive heart failure, unstable angina, or other vascular events. Major adverse events were defined as death, nonfatal myocardial infarction, or nonfatal stroke. Duke Activity Status Index metabolic equivalent tasks (DASI METs) are calculated as DASI score divided by 3.5 (see “Methods” section for details). Because of strong correlations among these variables, each was evaluated in a separate model that was adjusted for other independent predictors of all adverse events (race, history of dyslipidemia or diabetes or smoking, prior coronary artery disease [CAD], diastolic blood pressure, Women’s Ischemia Syndrome Evaluation [WISE] CAD severity score) and major adverse events (history of diabetes or smoking, prior CAD, high-sensitivity C-reactive protein level, hemoglobin level, WISE CAD severity score). CI indicates confidence interval; BMI, body mass index; and PEPI-Q, Postmenopausal Estrogen-Progestin Intervention questionnaire.

**FIGURE 2.** Proportion of Women With Adverse Events by Categories of Obesity and Fitness

Mean (SD) follow-up time was 3.9 (1.8) years. See FIGURE 1 legend for definitions of adverse events and abbreviations. Not obese was defined as BMI <30 and obese as BMI ≥30; fit was defined as DASI score ≥25 and not fit as DASI score <25.

Before adjusting for other significant predictors, both DASI and PEPI-Q scores were significantly associated with risks of all adverse events, major adverse events, and all-cause mortality (P<.01 for all). After adjusting for the other significant predictors of all adverse events, categorical DASI score less than 25 was associated with 46% increased risk of all adverse events (HR, 1.46; 95% CI, 1.10-1.94; P=.008). Furthermore, both DASI and PEPI-Q scores remained significant independent predictors of the risk of all adverse events and major adverse events (FIGURE 1) but not all-cause mortality (PEPI-Q: HR, 0.88; 95% CI, 0.74-1.03; P=.11; DASI METs: HR, 0.93; 95% CI, 0.87-1.01; P=.12), even after adjusting for significant risk predictors for adverse events (as listed above) including CAD severity score.

When divided into groups by categories of BMI and physical activity (FIGURE 2), women who had a BMI less than 30 and a DASI score of 25 or greater had the lowest proportion of all adverse events (23.9%, P=.001) or major adverse events (5.6%, P=.002) during follow-up. Women with a DASI score less than 25 had the highest risk of all adverse events or major adverse events regardless of BMI category. When these category groups were analyzed for survival free of all adverse events using Kaplan-Meier methods (FIGURE 3), women who had DASI scores of 25 or greater had significantly greater event-free survival than women with DASI scores less than 25, both for all adverse events and for major adverse events, regardless of BMI category.

When women with obstructive CAD were excluded from the adverse event analyses or when other anthropometric measures were used to categorize obesity (eg, waist-hip ratio), these categorical and continuous relationships with adverse events remained significant and relatively unchanged (data not shown). Likewise, when only women with severe CAD were analyzed, none of the anthropometric measures were related to adverse events, but DASI and...
PEPI-Q scores were still significant univariate predictors of all adverse events and major adverse events (data not shown).

COMMENT

Most studies of BMI and other measures of obesity have not adequately accounted for physical fitness, a known modifier of weight status and a potential mediator of the effects of obesity on CAD and adverse CV outcomes. Therefore, the independent contributions of BMI and fitness to CV health or disease have been unclear. Our study indicates that data from simple, self-reported questionnaires that estimate average physical activity and functional capacity are significantly associated with objective CV outcomes, including presence of angiographic CAD as well as risk of adverse CV events. Moreover, these associations are independent of anthropometric measurements and other CV risk predictors, including prior CAD or severity of angiographic CAD.

Thus, our findings suggest that self-reported level of physical activity and functional capacity are more important than weight status or body habitus for CV risk stratification in women. Although physical fitness was not directly measured in most women, the DASI and PEPI-Q scores have been shown in a WISE cohort substudy to correlate with fitness directly measured as exercise capacity by treadmill testing. Our data support previous studies showing that functional capacity appears to be more important than BMI for all-cause and CV mortality, especially in women, and we extend the predictive importance of fitness in women to include other adverse events including nonfatal MI and stroke in addition to mortality. Notably, adverse event rates in the WISE cohort are much higher than in the general population, as 8% of the women died, 13% had a major adverse CV event, and 38% had some adverse CV event during an average follow-up of less than 4 years.

Obesity is increasingly recognized as a public health epidemic and modifiable risk factor for CHD, but the prevalence of obesity has only increased in recent decades. Numerous studies that have not adequately measured fitness have shown that anthropometric indices are independently related to risk of CHD and CV events, and BMI in particular has become commonly used in clinical practice. We found that, despite its association with numerous CV risk factors including hypertension, diabetes, and the metabolic syndrome, BMI was a poor predictor of both baseline angiographic CAD as well as prospective risk of adverse events. When compared with BMI, indices of abdominal adiposity were all stronger predictors of obstructive angiographic CAD and risk of adverse events, consistent with prior studies. However, in contrast to DASI and PEPI-Q scores, anthropometric indices were not independently associated with obstructive CAD or adverse events after adjusting for other CV risk predictors. While our findings may underestimate the impact of obesity on CV risk because it is mediated by these other CV risk predictors, the self-reported fitness scores provided significant independent measures for risk stratification.

Many theories have been proposed to explain increased CV risk associated with obesity, such as the association of obesity with numerous risk mediators including traditional CV risk factors, insulin resistance, inflammation, and endothelial dysfunction. We demonstrate that excess weight is also associated with reduced physical activity and functional capacity, suggesting that the CV risk of obesity may be explained in part by the adverse effects of low fitness. Both weight loss and exercise have been shown to reduce levels of inflammatory markers in women and in patients with CHD. We found that higher physical fitness scores were related to lower levels of insulin, triglycerides, hs-CRP, and IL-6, so inflammation and insulin resistance could provide mechanistic links for the strong association of fitness with adverse events in this population of women. Therefore, the DASI and PEPI-Q provide simple, noninvasive assessments that encompass the interactions of multiple CV risk mediators within individual patients and that independently predict their CV outcomes.

Figure 3. Proportion of Women Free From All Adverse Events and Major Adverse Events During Follow-up, by Categories of Obesity and Fitness, Using Kaplan-Meier Methods

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Physical fitness has beneficial effects on numerous mediators of CV risk including obesity, so increased physical activity appears to be an ideal therapy for CHD. While weight loss has been shown to improve multiple CV risk factors, the direct benefit of therapy for CHD. While weight loss has been shown to reduce CV risk, however, physical activity has been shown to reduce CV risk. Many currently popular approaches to reduction of obesity, such as specific diets or bariatric surgery, do not directly measure improvements in physical fitness. Focusing on weight loss alone fails to directly address the related but more important lack of physical fitness among overweight individuals. The latest American Heart Association CV disease prevention guidelines for women have made accumulating a minimum of 30 minutes of moderate-intensity physical activity on most, and preferably all, days of the week a Class I recommendation for all risk groups. Thus, focusing on weight loss alone fails to directly address the related but more important lack of physical fitness among overweight individuals. The latest American Heart Association CV disease prevention guidelines for women have made accumulating a minimum of 30 minutes of moderate-intensity physical activity on most, and preferably all, days of the week a Class I recommendation for all risk groups. Thus, physical fitness assessment and intervention should be included in the management of all women at risk for CHD.

Limitations
Our prospective, observational study has inherent limitations regarding assessment of causality. Specifically, our reported associations between measures of fitness and adverse CV events may have been due to physical activity limitations from the observed higher prevalence of obstructive CAD rather than due to the low fitness levels, per se. However, our analyses showing DASI and PEPI-Q scores to be significant predictors despite adjusting for both prior CAD and WISE CAD severity score argue against this possibility, and analyses excluding patients with obstructive CAD continued to show the same relationships, although significance was reduced mainly due to reduced numbers of adverse CV events (data not shown).

We do not have access to more accurate indices of visceral adiposity such as dual-energy x-ray absorptiometry or computed tomography scans, but previous studies have shown that results of such scans are highly correlated with measures such as waist circumference and waist:hip ratio. We also do not have adequate dietary information to include in these analyses. In addition, our lack of independent associations between measures of obesity and CV outcomes may be confounded by adjusting for other independent predictors that are actually mediators of adverse effects of obesity on CV outcomes. Furthermore, we studied a relatively small population of symptomatic women, and the DASI and PEPI-Q scores are self-reported measures with potential source random error, although these scores have been validated in the WISE cohort. The PEPI-Q is a limited measure and could theoretically be affected by patients’ occupations or domestic situations, whereas the DASI includes more generally applicable activities from daily living or common recreation. Women lost to follow-up as result of an adverse event (eg, survival bias) may have contributed to underestimation of long-term adverse event rates and associations. Finally, our results using the DASI and PEPI-Q for CV risk prediction need to be confirmed in other large cohorts.

Conclusions
Among women referred for coronary angiography to evaluate suspected myocardial ischemia, we found that BMI, waist circumference, waist:hip ratio, and waist:height ratio were not independently associated with angiographic CAD or adverse CV events. However, lower self-reported physical fitness scores were associated with higher prevalence of CHD risk factors and angiographic CAD at baseline as well as higher risk of adverse events during intermediate-term follow-up, independent of both traditional CV risk factors as well as anthropometric indices. These results suggest that fitness may be more important than overweight or obesity for CV risk in women. Evaluation of physical activity and functional capacity using simple questionnaires should be an integral part of CV risk stratification, and interventions aimed at increasing physical fitness levels should be included in the management of all women at risk for CHD.

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Author Contributions: Dr Wessel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: Olson, Handberg, Sopko, Kelsey, Pepine, Bairey Merz. Acquisition of data: Reis, Handberg, Pepine, Bairey Merz. Analysis and interpretation of data: Wessel, Arant, Olson, Johnson, Sharaf, Shaw, Sopko, Kelsey, Pepine, Bairey Merz. Drafting of the manuscript: Wessel, Arant, Shaw, Pepine, Bairey Merz. Critical revision of the manuscript for important intellectual content: Wessel, Arant, Olson, Johnson, Reis, Sharaf, Shaw, Handberg, Sopko, Kelsey, Pepine, Bairey Merz. Statistical analysis: Olson, Johnson, Shaw. Obtained funding: Reis, Handberg, Kelsey, Pepine, Bairey Merz. Administrative, technical, or material support: Reis, Sharaf, Handberg, Pepine, Bairey Merz. Study supervision: Sopko, Kelsey, Pepine, Bairey Merz. Funding/Support: This study was supported by NHLBI contracts N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, U01-HL64829-01, U01-HL64914-01, and U01-HL64924-01, and by grants from the Gustavus and Louis Pfeiffer Research Foundation, Danville, III; the Women’s Guild of Cedars-Sinai Medical Center, Los Angeles, Calif; the Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh; and QMED Inc, Laurence Harbor, NJ.

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REFERENCES
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