Metacarpal Cortical Area and Risk of Coronary Heart Disease

The Framingham Study

Elizabeth J. Samelson1,2, Douglas P. Kiel1,2, Kerry E. Broe1, Yuqing Zhang3, L. Adrienne Cupples4, Marian T. Hannan1,2, Peter W. F. Wilson5,6, Daniel Levy6, Setareh A. Williams7, and Viola Vaccarino8

1 Research and Training Institute, Hebrew Rehabilitation Center for Aged, Boston, MA.
2 Division on Aging, Harvard Medical School, Boston, MA.
3 Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA.
4 Department of Biostatistics, Boston University School of Public Health, Boston, MA.
5 Department of Medicine, Boston University School of Medicine, Boston, MA.
6 Framingham Heart Study, Boston, MA, and National Heart, Lung, and Blood Institute, Bethesda, MD.
7 AstraZeneca LP, Wilmington, DE.
8 Department of Medicine, Division of Cardiology, Emory School of Medicine and Rollins School of Public Health, Atlanta, GA.

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The objective of this study was to determine the relation between bone mass and the incidence of coronary heart disease in women and men. Participants included 2,059 cohort members of the Framingham Study (1,236 women and 823 men aged 47–80 years) who underwent posteroanterior hand radiography and were free from cardiovascular disease at baseline (1967–1970) and who were then followed for 30 years through the end of 1997 for the incidence of coronary heart disease. The incidence of coronary heart disease decreased from 15.65/1,000 person-years among women in the lowest metacarpal cortical area quartile to 11.76/1,000 person-years among women in the highest quartile (ptrend = 0.03), and the inverse relation persisted after adjustment for confounders (highest vs. lowest quartile of metacarpal cortical area: hazard ratio = 0.73, 95% confidence interval: 0.53, 1.00; ptrend = 0.03). In contrast, no association was present in men (highest vs. lowest quartile of metacarpal cortical area: hazard ratio = 1.14, 95% confidence interval: 0.84, 1.56; ptrend = 0.55).

The relation between osteoporosis and mortality due to cardiovascular disease in women (1–3) and laboratory evidence linking atherosclerosis and bone metabolism (4–6) suggest that individuals with low bone mass may have an increased incidence of coronary heart disease. Although one study reported an inverse association between bone mineral density and stroke incidence in women (7), no study has examined bone mass in relation to the incidence of cardiovascular disease in women and men. If low bone mass and atherosclerosis share a common pathogenesis, then strategies for prevention of osteoporosis may, in turn, have implications for reduction of cardiovascular disease risk.

The purpose of this study was to evaluate the relation between bone mass, measured by relative metacarpal cortical area, and the incidence of coronary heart disease in middle-aged women and men.

MATERIALS AND METHODS

Study design and participants

The Framingham Study is a population-based cohort of 2,875 women and 2,334 men aged 28–62 years, who were examined biennially since 1948 (8). As part of an osteoporosis study, posteroanterior radiographs of the right hand were taken for 2,411 cohort members (1,394 women and 1,017 men) between 1967 and 1970. Cohort members were excluded from the present study if, at the time of hand radiography, they had a history of stroke, transient ischemic attack, congestive heart failure, intermittent claudication,
angina pectoris, coronary insufficiency, or myocardial infarction (158 women and 194 men). Participants (n = 2,059) were followed for a 30-year period from the time of hand radiography, defined as the baseline examination, through the end of 1997, the closing date for this study.

Assessment of bone mass

Radiogrammetry, based on hand radiographs taken in 1967–1970, was used to measure the cortical bone mass of the second metacarpal of the right hand. The second metacarpal was selected because it is one of the largest bones of the hand, has a more constant shape than the other metacarpals, and is approximately circular at the midshaft, with the medullary cavity nearly centered in the tubular bone cylinder (9, 10).

Two readers, unaware of the health status of participants, assessed cortical bone mass according to a standardized protocol. Hand radiographs were placed flat on a lighted viewing box, and measurements of cortical external width (R) and medullary width (r) were made with a digital caliper halfway up the second metacarpal (figure 1). Digital calipers were calibrated to the nearest 0.01 mm, and measurements were recorded to the nearest 0.1 mm. The relative metacarpal cortical area was calculated as 100 × (R² – r²)/R².

In order to assess reliability, 25 hand radiographs were randomly selected and provided to each of the two readers twice for blinded measurements. The intraobserver correlation coefficient was 0.99 for external width and 0.94 for medullary width. The interobserver correlation coefficients for external and medullary width were equal to the intraobserver coefficients.

Assessment of coronary heart disease

The incidence of coronary heart disease was defined as the first occurrence of recognized or unrecognized myocardial infarction (identified by electrocardiogram or enzymes), angina pectoris, coronary insufficiency, or coronary disease death during the period of follow-up. These diagnoses were based on the review of a three-member panel of physicians, who examined all available information including hospital records and death certificates (11, 12). Analyses were repeated for a more restrictive outcome, or “hard” coronary heart disease, defined as recognized myocardial infarction, coronary insufficiency, and coronary disease death.

Potential confounding variables

Information on covariates was based on data collected at, or prior to, the examination at the time of hand radiography. If not available, data from the examination closest in time to the hand radiography were used.

Age, education, menopausal status, age at menopause, surgical menopause, and estrogen use were assessed by questionnaire at the time of hand radiography. Height and weight were measured using a stadiometer and balance beam scale.

The number of cigarettes smoked per day was averaged over all the available examinations from the start of the Framingham Study through the examination of radiography. Alcohol consumption was computed by multiplying the average amount of alcohol in a single drink of beer, wine, or spirits by the average number of drinks per week reported at examinations in 1951–1954 and 1960–1964 (13).

Participants were asked, at examinations in 1954–1958 and 1971–1973, about the average number of hours per day performing “sedentary, slight, moderate, and heavy levels of physical activity” during work and leisure time and the average number of hours per day resting and sleeping. The hours spent at each level of activity were multiplied by a weight based on the oxygen consumption required for that activity and then summed to create an index of physical activity (14). The physical activity index was averaged for the two examinations.

At the time of radiography, systolic blood pressure (mmHg) was measured by a physician using a standard sphygmomanometer. Total serum cholesterol (mg/dl) was measured on blood drawn from nonfasting subjects using nonenzymatic methods (15).

Diabetes was defined as a casual glucose level of more than 150 mg/dl on two or more study visits or treatment with insulin or oral hypoglycemic agents reported up through the examination of radiograph.

High density lipoprotein cholesterol (mg/dl) was first measured in 1968–1971 according to the protocol of the Lipid Research Clinics Program (16).

Statistical analysis

Women and men were each stratified by 2-year age groups and assigned a bone mass quartile (1 = lowest) according to the sex-specific distribution of relative metacarpal cortical area for his/her age group. Characteristics of participants were compared across age-specific quartiles of metacarpal cortical area using analyses of variance for continuous variables and chi-square statistics for dichotomous variables.

The incidence of coronary heart disease was calculated as the number of cases divided by the number of person-years of follow-up time. For each individual, the number of person-years was determined from the date of hand radiog-
raphy to the date of the first of the following events: coronary heart disease, last contact, death, or December 31, 1997 (closing date for this study).

Cox proportional hazards regression was used to calculate hazard ratios and 95 percent confidence intervals for the relation between the age-specific quartile of relative metacarpal cortical area and the risk of coronary heart disease.

Factors known to be associated with the risk of coronary heart disease and/or bone mass were considered as potential confounders. To be retained in final multivariable models, selected variables had to be associated with coronary heart disease (p ≤ 0.10) or had to appreciably (≥ 10 percent) change the magnitude of the hazard ratio unadjusted for the variable (17).

Multivariable models included age (continuous), education (high school graduate, yes/no), body mass index (continuous), smoking (0, 1–9, ≥ 10 cigarettes/day for women; 0, 1–9, 10–19, ≥ 20 cigarettes/day for men), alcohol (0, 1–2, ≥ 2 ounces/week for women; 0, 1–2, 3–4, > 4 ounces/week for men; 1 ounce = 29.57 ml), systolic blood pressure (continuous), cholesterol (continuous), high density lipoprotein (tertiles), and diabetes (yes/no). Menopause age (continuous), surgical menopause (yes/no), and estrogen use (yes/no) were additionally adjusted in women. Individual indicator variables were created to represent whether or not information was missing for education (43 women, 35 men), high density lipoprotein cholesterol (313 women, 189 men), and, for women, oophorectomy (42 women). The p value for the test for trend was obtained by entering into the model an ordinal variable with each level representing the age-specific quartile of relative metacarpal cortical area.

RESULTS

At the time of radiography, the mean age of participants (1,236 women, 823 men) was 60 years and ranged from 47 to 80 years. The mean duration of follow-up was 20 years in women and 16 years in men and reached a maximum of 30 years. During the follow-up period, 320 women and 342 men developed coronary heart disease.

The mean weight and body mass index increased with age-specific quartile of relative metacarpal cortical area in women (table 1). Women in the lower quartiles of metacarpal cortical area were more likely to be current smokers than those in higher quartiles, while alcohol consumption and systolic blood pressure appeared to increase with quartile in women. The frequency of surgical menopause and bilateral oophorectomy did not differ with respect to metacarpal cortical area; however, those in the lower metacarpal cortical area quartiles were more likely to be postmenopausal and had an earlier age at menopause than those in the higher quartiles. Among women who used estrogen at the time of hand radiography, the duration of use was only slightly longer for those in the highest metacarpal cortical area quartile, 4.3 years, than for women in the lowest quartile, 3.7 years.

Similar to women, men in the higher quartiles of metacarpal cortical area were more frequently high school graduates than those in the lower quartiles (table 1). Men in the higher quartiles of metacarpal cortical area also appeared to be somewhat heavier and to have a greater frequency of diabetes compared with those in the lower quartiles, although no other trends were apparent. The physical activity level was unrelated to metacarpal cortical area in women and men.

The incidence rates of coronary heart disease decreased from 15.65/1,000 person-years among women in the lowest metacarpal cortical area quartile to 11.76/1,000 person-years among women in the highest quartile (table 2). The corresponding age-adjusted hazard ratio of coronary heart disease for women in the fourth quartile relative to those in the first quartile was 0.74 (95 percent confidence interval: 0.54, 1.01). The trend in decreasing coronary heart disease risk with increasing metacarpal cortical area was statistically significant in women (p = 0.03). In contrast, hazard ratios were slightly greater than 1.00 for the second through fourth quartiles of metacarpal cortical area in men. Furthermore, no trend (p = 0.51) was observed between the age-specific quartile of metacarpal cortical area and the risk of coronary heart disease in men.

Hazard ratios did not change appreciably with additional control of potential confounding variables for either women or men (table 2). For example, the multivariable-adjusted hazard ratio for women in the highest metacarpal cortical area quartile was 0.73 (95 percent confidence interval: 0.53, 1.00) and was similar in magnitude to the age-adjusted hazard ratio of 0.74 (95 percent confidence interval: 0.54, 1.01). Although the test for linear trend in adjusted hazard ratios with metacarpal cortical area quartile was statistically significant (p = 0.03), the reduction in coronary heart disease risk, slightly more than 25 percent, was similar in women in the highest third (hazard ratio = 0.71, 95 percent confidence interval: 0.52, 0.97) and fourth (hazard ratio = 0.73, 95 percent confidence interval: 0.53, 1.00) quartiles. No trend in decreasing coronary heart disease risk with metacarpal cortical area was observed in men (highest vs. lowest quartile: multivariable-adjusted hazard ratio = 1.14, 95 percent confidence interval: 0.84, 1.56; p_trt = 0.55).

Multivariable-adjusted hazard ratios were unchanged in women following additional adjustment for reproductive factors including menopause age, surgical menopause, and estrogen use (results not shown). Excluding premenopausal women (n = 111 or 9 percent) had no effect on results. Using a more restrictive definition of coronary heart disease did not affect the results, although confidence intervals were slightly wider because of the reduced number of cases. For example, the adjusted hazard ratio for “hard” coronary heart disease was 0.73 (95 percent confidence interval: 0.48, 1.10) for women in the highest quartile of metacarpal cortical area and identical to the hazard ratio for the more broad definition of coronary heart disease.

DISCUSSION

This long-term, prospective study found that women with a higher level of metacarpal cortical area have a decreased rate of coronary heart disease relative to those with lower levels of metacarpal cortical area. The inverse relation was independent of age, education, smoking, alcohol, systolic blood pressure, lipids, diabetes, and menopausal history.
## TABLE 1. Comparison of baseline characteristics in women and men according to age-specific quartile of relative metacarpal cortical area, Framingham Osteoporosis Study, 1967–1970

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quartile of relative metacarpal cortical area*</td>
<td>P\text{\textsubscript{trend}}</td>
<td>Quartile of relative metacarpal cortical area</td>
<td>P\text{\textsubscript{trend}}</td>
</tr>
<tr>
<td></td>
<td>1 (n = 301)</td>
<td>2 (n = 311)</td>
<td>3 (n = 317)</td>
<td>4 (n = 307)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.2</td>
<td>60.2</td>
<td>60.1</td>
<td>60.2</td>
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<tr>
<td>High school graduate (%)</td>
<td>60.6</td>
<td>65.0</td>
<td>70.5</td>
<td>69.4</td>
</tr>
<tr>
<td>Height (inches)</td>
<td>62.6</td>
<td>62.8</td>
<td>62.9</td>
<td>62.6</td>
</tr>
<tr>
<td>Weight (pounds†)</td>
<td>138.7</td>
<td>140.7</td>
<td>144.4</td>
<td>145.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3</td>
<td>25.6</td>
<td>26.2</td>
<td>26.5</td>
</tr>
<tr>
<td>Smoking (cigarettes/day)</td>
<td>7.3</td>
<td>5.8</td>
<td>5.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>38.9</td>
<td>33.1</td>
<td>31.2</td>
<td>30.9</td>
</tr>
<tr>
<td>Alcohol (ounces†/week)</td>
<td>1.9</td>
<td>2.1</td>
<td>2.4</td>
<td>2.5</td>
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<tr>
<td>Physical activity index</td>
<td>31.6</td>
<td>31.9</td>
<td>31.8</td>
<td>31.7</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136.7</td>
<td>139.2</td>
<td>138.4</td>
<td>140.8</td>
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<tr>
<td>Total cholesterol (mg/dl)</td>
<td>240.9</td>
<td>242.2</td>
<td>245.5</td>
<td>242.0</td>
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<tr>
<td>High density lipoprotein cholesterol (mg/dl)</td>
<td>57.3</td>
<td>56.3</td>
<td>58.1</td>
<td>58.1</td>
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<tr>
<td>Diabetes (%)</td>
<td>4.0</td>
<td>3.5</td>
<td>5.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>94.0</td>
<td>92.9</td>
<td>92.1</td>
<td>85.3</td>
</tr>
<tr>
<td>Surgical menopause (%)</td>
<td>28.7</td>
<td>28.6</td>
<td>29.3</td>
<td>28.7</td>
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<tr>
<td>Age at menopause (years)‡</td>
<td>48.6</td>
<td>48.8</td>
<td>49.6</td>
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<tr>
<td>Bilateral oophorectomy (%)</td>
<td>18.7</td>
<td>17.8</td>
<td>18.0</td>
<td>16.9</td>
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<tr>
<td>Estrogen use (%)§</td>
<td>4.4</td>
<td>8.9</td>
<td>12.3</td>
<td>15.2</td>
</tr>
<tr>
<td>Estrogen use (years)§</td>
<td>0.5</td>
<td>0.7</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Estrogen use users (years)¶</td>
<td>3.7</td>
<td>3.4</td>
<td>4.2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* Quartiles are numbered from the lowest (quartile 1) to the highest (quartile 4).
† Metric equivalents: 1 inch = 2.54 cm; 1 pound = 0.45 kg; 1 ounce = 29.57 ml.
‡ Among women with natural menopause.
§ Among postmenopausal women.
¶ Among women who ever used estrogen.

Others have found that postmenopausal women with low bone mineral density (1, 2), bone loss (3), and fracture (2) have increased mortality due to cardiovascular causes. However, since death certificates have limited reliability for accurately classifying cardiovascular death in elderly persons (18), the current study, which used standardized clinical examinations, laboratory tests, and hospital record reviews to ascertain incident cardiovascular disease, provides new evidence connecting osteoporosis and atherosclerosis.

The inverse relation between bone mass and coronary heart disease risk in women found in this study is supported by reports that postmenopausal women with low bone mineral density (19, 20) or with greater amounts of bone loss (21, 22) have greater prevalence and severity of aortic calcification, a predictor of cardiovascular disease incidence and mortality (23). These observations, in addition to laboratory investigations, suggest that atherosclerosis and osteoporosis may share a common pathogenesis. Bone matrix proteins, such as osteopontin (4), osteocalcin (5), and bone morphogenetic protein (6), have been found in atherosclerotic plaques. Several risk factors for cardiovascular disease, including interleukin-6 and homocysteine, as well as statin drugs used to treat hyperlipoproteinemia (24–26), have potential links to osteoporosis (27). In addition, regulators of bone resorption, such as vitamin D (28) and osteoprotegerin (29), have been associated with vascular calcifications.

The inverse association between cortical bone mass and coronary heart disease incidence observed in women in this study was not present in men. The difference in results for women and men in this study is congruent with the difference reported in a previous study of Framingham participants, which found that 25-year metacarpal cortical area bone loss was associated with greater 25-year aortic calcification in women, but not in men, after adjustment for confounders (30). Previous studies of osteoporosis and cardiovascular mortality did not include men (or did not report results specifically for men (31)). Nevertheless, several possible explanations are offered to explain the difference in results for women and men.

The presence of an association between metacarpal cortical area and coronary heart disease in women and the absence of such a relation in men may reflect some sex-specific differences in the underlying pathophysiology of bone mineralization, cardiovascular disease, or both. It is important to note that the metacarpal cortical area is deter-
mined from the difference in measurements of the total external width and the internal medullary width (figure 1). Women may lose more or even the same amount of bone as men at the endosteal inner surface. Men, however, gain more bone periosteally at the outer surface than do women (32). As a result, the difference between the total and inner widths may be a greater reflection of the amount of cortical thinning in women than in men (32, 33). Thus, in older women, variability in relative metacarpal cortical area may be more a function of underlying hormonal factors (34, 35) while, in men, it may be more a reflection of bone size. If osteoporosis and atherosclerosis share a common pathogenesis, the ability to detect an association in men should be improved by using a direct measure of bone mass. This study, however, was limited by the technology available in the late 1960s, prior to the development of modern bone measurement techniques.

Some differences in the physiologic processes, epidemiology, and the clinical presentation and outcomes in women and men with coronary heart disease have been reported (36–44). As a result, analyses were repeated using the more definitive “hard” coronary heart disease outcomes. These included recognized myocardial infarction, coronary insufficiency, and coronary disease death, which may be diagnosed more precisely than the more broadly defined outcome of coronary heart disease. The findings were similar to those reported for the broad definition of coronary heart disease presented herein, although statistical precision was slightly reduced.

The strengths and weaknesses of this study warrant mention. Participants were selected from a population-based sample, included both women and men, and were observed over three decades of follow-up time. Further, this prospective study was the first investigation of bone mass in relation to incidence (in contrast to mortality) of coronary heart disease, using highly reliable and valid case ascertainment methods. However, the long duration of follow-up would not have been possible without the use of the earlier technology of bone mass assessment using radiogrammetry. Although bone mass was determined from a single measurement of cortical area based upon plain hand films, the relative metacarpal cortical area has been used to predict risk of hip fracture in this cohort (21) as well as in others (45, 46). The metacarpal cortical area has also been shown to predict several other outcomes in cohort members of the Framingham Study, including lumbar aortic calcification (30) and the incidence of breast (47), colon (48), and prostate (49) cancer.

The inverse relation between the metacarpal cortical area and the incidence of coronary heart disease observed in women might suggest that efforts to reduce the risk of osteoporosis may decrease the risk of coronary disease in women. However, in order to draw definitive conclusions regarding the implications of these findings on the treatment or prevention of osteoporosis, we need prospective studies that use current bone densitometry measures and include both women and men to help elucidate the etiologies of these two important diseases.

acknowledgments

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