

# Short Stature and Risk for Mortality and Cardiovascular Disease Events

## The Framingham Heart Study

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**Background** Several studies have observed an inverse association between height and risk for coronary disease, but it is unclear whether other traditional coronary disease risk factors may have confounded this association. We examined the original Framingham Heart Study cohort to determine whether short stature is associated with all-cause mortality, cardiovascular disease mortality, and myocardial infarction after adjusting for age and other traditional coronary heart disease risk factors.

**Methods and Results** A total of 2019 men and 2585 women were followed up to 35.6 years. Subjects were stratified by sex and divided into quartiles according to height. Risk ratios were calculated from proportional hazards analyses comparing the first, second, and third quartiles of height to the tallest quartile before and after adjusting for age, hypertension, smoking,

serum cholesterol, diabetes, relative weight, and alcohol intake. In both sexes, there were significant differences in the unadjusted event rates between the shortest and the tallest quartile for all-cause mortality, cardiovascular mortality, and myocardial infarction. Once the analyses were age adjusted, differences among height quartiles persisted only for risk of myocardial infarction in women. Further adjustment for other clinical variables had little additional impact on the results.

**Conclusions** After considering age and other coronary disease risk factors, short stature was not associated with increased risk for all-cause or cardiovascular mortality in either sex. It was associated with increased risk for myocardial infarction in women but not in men. (*Circulation*. 1994;90:2241-2247.)

**Key Words** • height • mortality • cardiovascular disease • infarction

For several decades, investigators have been trying to determine whether body habitus is associated with risk for cardiovascular disease. Earlier studies emphasized the relation between obesity and risk for coronary disease, but several studies also observed an increased risk for coronary disease in shorter men.<sup>1-5</sup> Some of these earlier studies did not adjust for other traditional coronary disease risk factors that may have confounded the observed inverse association between height and coronary disease incidence. Recently, there has been renewed interest in the association of short stature with risk for coronary disease. The Physicians' Health Study reported results showing that shorter physicians were at increased risk for myocardial infarctions compared with their taller counterparts after controlling for traditional coronary disease risk factors.<sup>5</sup>

The Framingham Heart Study offers an opportunity to determine whether short stature is associated with increased risk for all-cause mortality, cardiovascular mortality, or myocardial infarction independent of traditional coronary disease risk factors in a population-based sample that has been routinely followed for more than 35 years.

## Methods

### Study Population

In 1948, the US Public Health Service undertook a longitudinal study to investigate precursors of cardiovascular disease. The Framingham Heart Study enrolled 5209 adults between the ages of 28 and 62 years from Framingham, Mass, and performed biennial examinations that included a detailed medical history, physical examination, 12-lead ECG, and laboratory tests.

The second Framingham Heart Study clinic examination (1951 through 1954) was used as the starting point for the present study to incorporate cholesterol data obtained at that examination cycle. Data for age, diabetes mellitus, hypertension, cholesterol, weight, and alcohol use were obtained from the second examination cycle, whereas data on height and smoking were obtained from the first clinic examination. Patients were excluded from the present analysis if they fulfilled any of the following criteria (1) died before the second examination, (2) did not attend the second examination cycle, (3) had prevalent cardiovascular disease at the second examination, (4) were missing height data, and (5) were lost to follow-up at the second examination.

### Measurements

Standing height was measured to the nearest 0.25 in after subjects removed their shoes. Framingham relative weight was used as an obesity index instead of body mass index (BMI) or metropolitan relative weight (MRW), because it was the obesity estimate that was least correlated with height.

### Framingham relative weight

$$= 100 \times (\text{Subject's weight} / \text{Median weight for sex-height group})$$

Serum cholesterol was measured by the method of Abell et al.<sup>6</sup> A subject was defined as hypertensive if he or she had a systolic pressure of  $\geq 160$  mm Hg or a diastolic pressure of  $\geq 95$

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mm Hg on each of two physician blood pressure measurements or was receiving medication for the treatment of high blood pressure. A subject was defined as diabetic if he or she had an abnormal glucose tolerance test, a random glucose level of  $>8.3$  mmol/L (150 mg/dL) on at least two occasions, or was under treatment for diabetes mellitus. Cigarette smoking was recorded as the average number of cigarettes smoked daily in the year before the examination, and alcohol use was recorded as the average number of ounces of alcohol consumed per week in the year before the examination. The formula used to calculate the amount of alcohol in a particular beverage has been described elsewhere.<sup>7</sup>

## Outcome Events

The three outcomes of interest were all-cause mortality, cardiovascular disease mortality, and myocardial infarction. Mortality data were obtained from hospital and physician records, autopsy findings, death certificates, and interviews with family members. Cardiovascular disease was defined as coronary heart disease (angina pectoris, coronary insufficiency, myocardial infarction, or coronary death), stroke, congestive heart failure, or intermittent claudication. The criteria used to define these entities have been described elsewhere.<sup>8-12</sup> Outcome events occurring between examination cycles 2 and 19 were included in this study and represent up to 35.6 years of follow-up.

## Analyses

Subjects were separated by sex and divided into quartiles according to height. To compare patient characteristics among height quartiles, the direct method of age adjusting was used for proportions, whereas age-adjusted least-squares methods were used for continuous variables (based on SAS procedures FREQ<sup>13</sup> and GLM<sup>14</sup>). Cox proportional hazards regression<sup>15</sup> was used to analyze the time to each outcome event and to estimate and compare risks among height quartiles (SAS procedure PH REG<sup>16</sup>). For each outcome, a simultaneous test of equal hazards in all quartiles was made using the Wald statistic.<sup>16</sup> A two-tailed significance level of  $P<.05$  was used in each case. Analyses were performed before and after adjusting for age, hypertension (0, no; 1, yes), cigarette smoking, serum cholesterol, diabetes (0, no; 1, yes), relative weight, and alcohol intake. Ninety-five percent confidence intervals were calculated for the risk ratios comparing the first, second, and third quartiles of height to the tallest one. Life-table survival analyses (SAS procedure LIFETEST<sup>14</sup>) were performed to produce age-adjusted plots by height quartiles for time to myocardial infarction. To accommodate changing values of risk factors over time, we performed the following time-dependent analysis. Follow-up and end points were apportioned among three consecutive 10-year periods (follow-up was truncated at 30 years), with successive intervals for a subject beginning with dates of attendance at biennial examinations 2, 7, and 12, respectively. Age and risk factor data recorded at these index examinations were applied only to the corresponding 10-year follow-up intervals (except baseline height quartile, which was taken as a fixed value across time). If a subject had a positive history for cardiovascular disease at an index examination, his or her subsequent time intervals were excluded from analysis. Sex-specific proportional hazards models were fitted that included height quartile and risk factors noted above; they were stratified by 10-year age group and by 10-year time period. Estimation and testing of hazards ratios among height quartiles proceeded as described previously.

## Results

### Patient Characteristics

Of the 5209 individuals who entered the study at examination 1, a total of 605 (11.6%) were excluded

from the present analysis. Thirty-three died before examination 2, 384 were alive but did not attend the second examination, 179 had evidence of cardiovascular disease at examination 2, 6 had missing height data, and 3 were lost to follow-up at examination 2. The final sample for this study included 4604 persons (2019 men and 2585 women). The mean age was  $45.7\pm 8.5$  years (range, 31 to 65 years) in men and  $46.0\pm 8.5$  years (range, 31 to 64 years) in women.

In men, there were 1200 deaths, 574 of which occurred as a result of cardiovascular disease over a median follow-up of 29.9 years (range, 0.18 to 35.4 years). New myocardial infarctions occurred in 504 men, at a median follow-up of 27.2 years (range, 0.05 to 35.4 years). In women, there were 1154 deaths, 473 of which occurred as a result of cardiovascular disease over a median follow-up of 33.4 years (range, 0.64 to 35.6 years). There were 281 new myocardial infarctions in women, at a median follow-up of 33.3 years (range, 0.54 to 35.6 years).

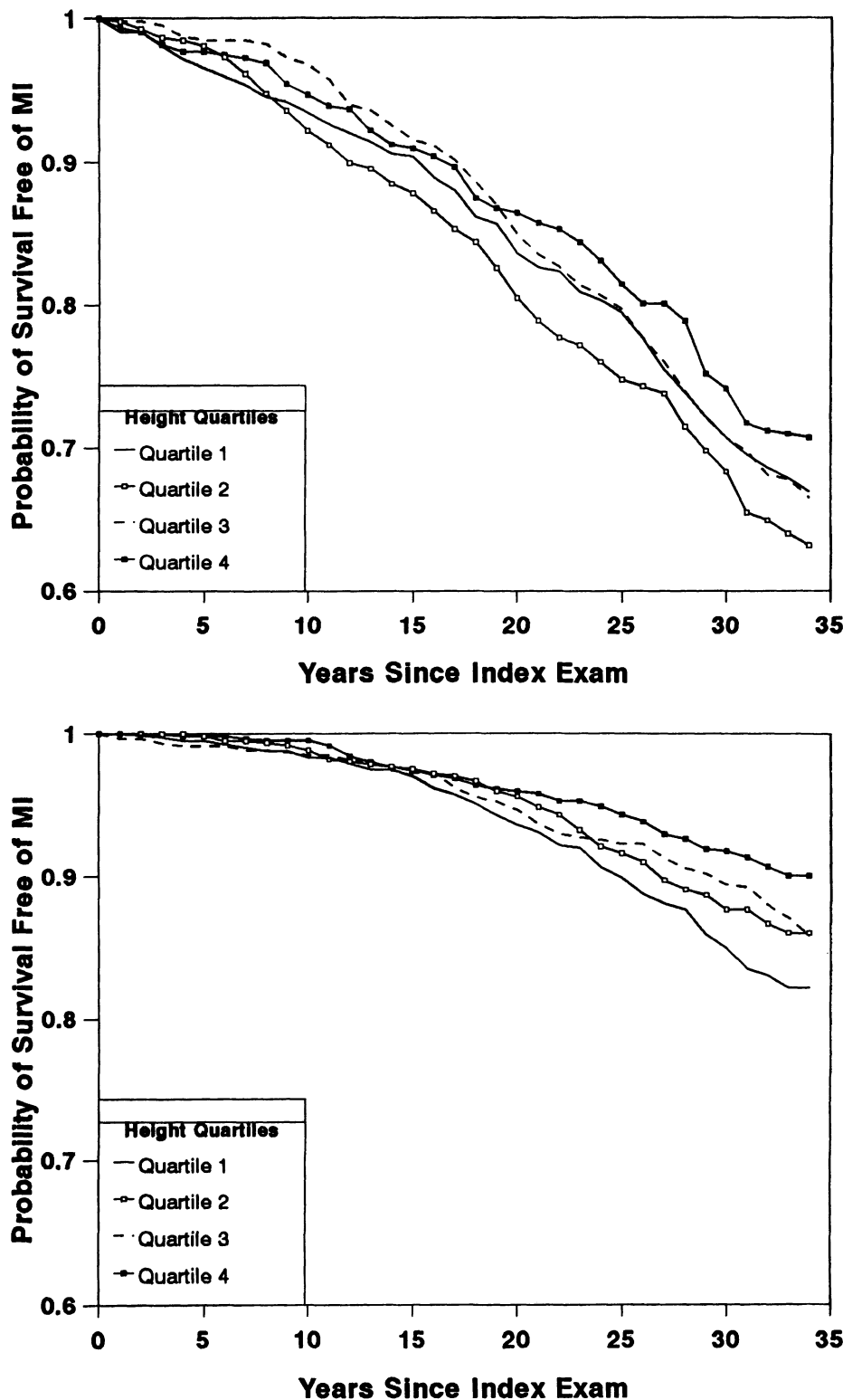
The mean height was  $67.6\pm 2.7$  in men and  $62.6\pm 2.4$  in women. In men, most of the clinical characteristics did not significantly differ among height quartiles (Table 1). The notable exception was age; shorter men were older than taller men ( $48.0$  versus  $43.5$  years in quartile 1 versus quartile 4,  $P<.001$ ). In women, several risk factors were significantly different among height groups (Table 1). Hypertension, relative weight, and diabetes mellitus were the only risk factors analyzed in women that did not differ among height quartiles.

## Outcome Events

In men, the unadjusted event rates differed significantly among height quartiles (Table 2a). The shortest quartile experienced higher rates for all-cause mortality (risk ratio, 1.51; 95% confidence interval [CI], 1.28 to 1.78), cardiovascular mortality (risk ratio, 1.42; 95% CI, 1.12 to 1.80), and myocardial infarctions (risk ratio, 1.30; 95% CI, 1.01 to 1.68) compared with the tallest quartile. However, once the data were age and risk factor adjusted, the quartiles were not significantly different. The age- and risk factor-adjusted risk ratio for the shortest versus the tallest quartiles was 1.01 (95% CI, 0.85 to 1.21) for all-cause mortality, 0.95 (95% CI, 0.74 to 1.22) for cardiovascular mortality, and 1.07 (95% CI, 0.81 to 1.39) for myocardial infarction.

Similar results were observed in women (Table 2b). The unadjusted risk ratio comparing the shortest to the tallest quartile was 1.35 (95% CI, 1.14 to 1.59) for all-cause mortality, 1.70 (95% CI, 1.31 to 2.21) for cardiovascular mortality, and 2.02 (95% CI, 1.43 to 2.87) for myocardial infarction. Differences among height quartiles for all-cause and cardiovascular mortality were not statistically significant after age and risk factor adjustments were made. However, for myocardial infarction, risk remained higher in the shortest compared with the tallest quartile (risk ratio, 1.86; 95% CI, 1.29 to 2.69) after adjustment for age and other traditional coronary disease risk factors.

It is possible that over the 35-year observation period of this study risk factors changed disproportionately in shorter or taller subjects. To assess the impact of differential risk factor changes over time, a time-dependent analysis was carried out (Table 3). The results of these analyses were nearly identical to those presented



Top, Age-adjusted life-table analysis for survival free of myocardial infarction (MI) according to height quartiles in men with a median follow-up of 27.2 years. Quartile 1, 56.0 to 65.75 in; quartile 2, 66.0 to 67.75 in; quartile 3, 68.0 to 69.5 in; and quartile 4, 69.75 to 76.5 in. There was no significant difference in survival free of MI among height quartiles ( $P=.13$ ). Bottom, Age-adjusted life-table analysis for survival free of MI according to height quartiles in women with a median follow-up of 33.3 years. Quartile 1, 51.5 to 61.0 in; quartile 2, 61.25 to 62.5 in; quartile 3, 62.75 to 64.25 in; and quartile 4, 64.5 to 70.75 in. There was a significant difference among height quartiles in survival free of MI ( $P=.01$ ).

in Table 2. Life-table plots for myocardial infarction are presented in the Figure.

### Discussion

For several decades, there has been considerable interest in identifying precursors of coronary heart disease. In addition to traditional risk factors such as

hypercholesterolemia, smoking, hypertension, and diabetes, several studies have examined the contribution of body habitus to risk for morbidity and mortality. In our study, short stature was not an independent predictor of all-cause mortality or cardiovascular mortality. It only emerged as a predictor of myocardial infarction in women.

TABLE 1. Baseline Characteristics of Men and Women According to Height

|                     | Height Quartile |            |             |            |       |
|---------------------|-----------------|------------|-------------|------------|-------|
|                     | Quartile 1      | Quartile 2 | Quartile 3  | Quartile 4 | P     |
| Men                 |                 |            |             |            |       |
| Inches              | 56.0-65.75      | 66.0-67.75 | 68.0-69.5   | 69.75-76.5 |       |
| Age, y              | 48.0            | 45.8       | 45.4        | 43.5       | <.001 |
| Cholesterol, mmol/L | 5.90            | 5.82       | 5.87        | 6.05       | .32   |
| Relative weight     | 102             | 102        | 102         | 102        | .91   |
| Hypertension, %     | 16.0            | 14.2       | 12.7        | 14.0       | .51   |
| Diabetes, %         | 3.0             | 2.4        | 1.9         | 1.7        | .46   |
| Cigarettes/d        | 12.5            | 13.4       | 13.9        | 11.8       | .08   |
| Alcohol, oz/wk      | 5.5             | 5.4        | 6.2         | 5.3        | .33   |
| Women               |                 |            |             |            |       |
| Inches              | 51.5-61.0       | 61.25-62.5 | 62.75-64.25 | 64.5-70.75 |       |
| Age, y              | 47.5            | 46.1       | 45.5        | 44.7       | <.001 |
| Cholesterol, mmol/L | 6.13            | 6.05       | 5.98        | 5.92       | .004  |
| Relative weight     | 102             | 104        | 105         | 104        | .91   |
| Hypertension, %     | 16.0            | 15.5       | 15.3        | 14.0       | .79   |
| Diabetes, %         | 1.5             | 1.5        | 2.5         | 1.3        | .46   |
| Cigarettes/d        | 3.9             | 5.1        | 4.8         | 5.7        | <.001 |
| Alcohol, oz/wk      | 1.5             | 1.8        | 1.9         | 2.2        | .006  |

All values except age are age-adjusted means or age-adjusted percent prevalences.

Case-control studies comparing patients with myocardial infarction with control subjects in the 1950s and 1960s noted an association of short stature in men with risk for coronary heart disease. Gertler and colleagues<sup>1</sup> reported that the mean height in patients with myocardial infarction was 4.8 cm less than in a control group. In another case-control study, Paffenbarger et al<sup>2</sup> noted similar differences. Multivariable analyses were not performed to evaluate the independent contribution of height to myocardial infarction risk in either of these studies. More recently, Palmer et al<sup>17</sup> reported in a case-control study of women under 65 years of age that the shortest women (<150 cm) were at greatest risk for myocardial infarction after controlling for body mass index, years of education, religion, and major coronary disease risk factors. Several large prospective studies from Britain examined the association of height with coronary disease incidence.<sup>3,4,18</sup> Marmot et al<sup>4</sup> examined 17 530 British civil servants over 7.5 years of follow-up and found that mortality was highest in men shorter than 168 cm. In that study, height continued to be a significant predictor of mortality after adjustments were made for blood pressure, cholesterol, smoking, body mass index, blood glucose, and age.

Recently, results from two investigations have suggested an inverse relation between height and risk for coronary heart disease. After 5 years of follow-up, the Physicians' Health Study reported that the tallest quintile of 22 071 male physicians had a 35% lower risk for myocardial infarction compared with the shortest quintile after adjusting for age, body mass index, smoking, hypertension, diabetes, family history of myocardial

infarction, alcohol intake, hypercholesterolemia, angina, and exercise frequency.<sup>5</sup> Yarnell et al<sup>19</sup> studied 4860 men in England with 4 years of follow-up and reported that the shortest quintile of men had twice as many myocardial infarcts as the tallest after adjusting for age, social class, and smoking.

In our study, the shortest individuals had significantly higher overall death rates and mortality from cardiovascular disease. However, most of the difference in death rates was due to an inverse association between height and age. The mean age of the shortest height quartile of men was 4.5 years greater than the tallest height quartile. In women, the corresponding difference in mean age was 2.8 years. Differences in age between height groups can be explained by height loss with aging or a secular trend toward increasing height in the population. Beginning at about age 40, humans gradually lose height due to a decrease in bone mineral density, osteoporosis, disk deterioration, postural changes, and spine deformities.<sup>20,21</sup> Second, there has been a secular change in height; individuals in the 1880s were on the average 4 in shorter than individuals in the 1950s.<sup>22</sup> This change is attributed to better nutrition, immunizations, and improved treatment of diseases of childhood. Some have suggested that the secular trend toward increasing height has ended,<sup>23</sup> but for our population height was measured in the 1950s in individuals born anywhere from the 1890s to the 1920s; secular trends probably are a factor.

Our finding of no association between height and risk for myocardial infarction in men is a departure from other recent well-designed trials.<sup>4,5</sup> Perhaps in the 1950s height was not a significant predictor of mortality due to

TABLE 2. Risk for Outcome Event in Men and Women According to Height

| Outcome                          | Quartile 1       | Quartile 2       | Quartile 3       | Quartile 4 | P*    |
|----------------------------------|------------------|------------------|------------------|------------|-------|
| <b>a. Men</b>                    |                  |                  |                  |            |       |
| All-cause mortality              |                  |                  |                  |            |       |
| No. of events                    | 346              | 325              | 295              | 234        |       |
| Risk ratios†                     |                  |                  |                  |            |       |
| Unadjusted                       | 1.51 (1.28-1.78) | 1.30 (1.10-1.54) | 1.28 (1.08-1.53) | 1          | <.001 |
| Age adjusted                     | 1.05 (0.88-1.24) | 1.09 (0.92-1.30) | 1.14 (0.96-1.36) | 1          | .44   |
| Age and covariate adjusted       | 1.01 (0.85-1.21) | 1.10 (0.93-1.31) | 1.10 (0.93-1.32) | 1          | .49   |
| Cardiovascular disease mortality |                  |                  |                  |            |       |
| No. of events                    | 164              | 151              | 143              | 116        |       |
| Risk ratios                      |                  |                  |                  |            |       |
| Unadjusted                       | 1.42 (1.12-1.80) | 1.21 (0.95-1.54) | 1.25 (0.97-1.59) | 1          | .04   |
| Age adjusted                     | 0.99 (0.77-1.26) | 1.02 (0.80-1.30) | 1.10 (0.86-1.40) | 1          | .81   |
| Age and covariate adjusted       | 0.95 (0.74-1.22) | 1.03 (0.81-1.33) | 1.08 (0.84-1.40) | 1          | .73   |
| Myocardial infarction            |                  |                  |                  |            |       |
| No. of events                    | 133              | 154              | 114              | 103        |       |
| Risk ratios                      |                  |                  |                  |            |       |
| Unadjusted                       | 1.30 (1.01-1.68) | 1.42 (1.10-1.82) | 1.13 (0.86-1.47) | 1          | .03   |
| Age adjusted                     | 1.12 (0.86-1.46) | 1.32 (1.03-1.70) | 1.07 (0.82-1.39) | 1          | .13   |
| Age and covariate adjusted       | 1.07 (0.81-1.39) | 1.30 (1.01-1.68) | 1.04 (0.79-1.37) | 1          | .15   |
| <b>b. Women</b>                  |                  |                  |                  |            |       |
| All-cause mortality              |                  |                  |                  |            |       |
| No. of events                    | 341              | 302              | 265              | 246        |       |
| Risk ratios                      |                  |                  |                  |            |       |
| Unadjusted                       | 1.35 (1.14-1.59) | 1.22 (1.03-1.44) | 1.08 (0.91-1.29) | 1          | <.01  |
| Age adjusted                     | 1.11 (0.94-1.31) | 1.11 (0.93-1.31) | 1.09 (0.91-1.30) | 1          | .61   |
| Age and covariate adjusted       | 1.13 (0.95-1.34) | 1.10 (0.92-1.31) | 1.10 (0.92-1.31) | 1          | .56   |
| Cardiovascular disease mortality |                  |                  |                  |            |       |
| No. of events                    | 157              | 125              | 102              | 89         |       |
| Risk ratios                      |                  |                  |                  |            |       |
| Unadjusted                       | 1.70 (1.31-2.21) | 1.39 (1.06-1.82) | 1.15 (0.87-1.53) | 1          | <.01  |
| Age adjusted                     | 1.35 (1.04-1.76) | 1.23 (0.94-1.62) | 1.14 (0.86-1.52) | 1          | .14   |
| Age and covariate adjusted       | 1.34 (1.02-1.75) | 1.22 (0.92-1.61) | 1.06 (0.79-1.42) | 1          | .13   |
| Myocardial infarction            |                  |                  |                  |            |       |
| No. of events                    | 98               | 72               | 64               | 47         |       |
| Risk ratios                      |                  |                  |                  |            |       |
| Unadjusted                       | 2.02 (1.43-2.87) | 1.51 (1.05-2.18) | 1.37 (0.94-2.00) | 1          | <.01  |
| Age adjusted                     | 1.79 (1.26-2.54) | 1.42 (0.98-2.05) | 1.36 (0.93-1.98) | 1          | .01   |
| Age and covariate adjusted       | 1.86 (1.29-2.69) | 1.44 (0.98-2.12) | 1.35 (0.91-2.00) | 1          | <.01  |

\*P value from test of equality among quartiles.

†Relative risks with 95% confidence intervals.

the high prevalence of other risk factors, particularly smoking, untreated hypertension, and hypercholesterolemia. In addition, we were unable to adequately adjust for two potential confounders: socioeconomic status and ethnic background. Today, with better prevention and treatment of these risk factors, height may emerge as a significant predictor of coronary disease.

Shorter stature in women was associated with increased risk for myocardial infarction. Women have been noted to have higher surgical mortality from coronary artery bypass surgery than men.<sup>24</sup> It has been postulated that women are more prone to coronary artery bypass graft occlusion since they have narrower coronary arteries. In the Coronary Artery Surgery

**TABLE 3. Time-Dependent Covariate Analysis: Association of Height Quartiles With Outcome**

|                                  | Quartile 1          | Quartile 2          | Quartile 3          | Quartile 4 |
|----------------------------------|---------------------|---------------------|---------------------|------------|
| <b>Men</b>                       |                     |                     |                     |            |
| All-cause mortality              |                     |                     |                     |            |
| No. of events                    | 237                 | 223                 | 187                 | 165        |
| Risk ratios (95% CI)             | 0.96<br>(0.77-1.19) | 1.01<br>(0.81-1.26) | 0.88<br>(0.70-1.12) | 1          |
| Cardiovascular disease mortality |                     |                     |                     |            |
| No. of events                    | 118                 | 111                 | 97                  | 87         |
| Risk ratios (95% CI)             | 0.85<br>(0.62-1.15) | 0.92<br>(0.67-1.25) | 0.84<br>(0.61-1.16) | 1          |
| Myocardial infarction            |                     |                     |                     |            |
| No. of events                    | 117                 | 127                 | 93                  | 86         |
| Risk ratios (95% CI)             | 1.16<br>(0.85-1.59) | 1.26<br>(0.93-1.71) | 0.94<br>(0.68-1.31) | 1          |
| <b>Women</b>                     |                     |                     |                     |            |
| All-cause mortality              |                     |                     |                     |            |
| No. of events                    | 195                 | 183                 | 165                 | 139        |
| Risk ratios (95% CI)             | 1.05<br>(0.81-1.34) | 1.14<br>(0.89-1.46) | 1.25<br>(0.97-1.61) | 1          |
| Cardiovascular disease mortality |                     |                     |                     |            |
| No. of events                    | 96                  | 85                  | 74                  | 52         |
| Risk ratio (95% CI)              | 1.19<br>(0.81-1.26) | 1.35<br>(0.92-1.98) | 1.40<br>(0.94-2.08) | 1          |
| Myocardial infarction            |                     |                     |                     |            |
| No. of events                    | 74                  | 57                  | 47                  | 38         |
| Risk ratio (95% CI)              | 1.72<br>(1.11-2.66) | 1.28<br>(0.80-2.02) | 1.19<br>(0.73-1.93) | 1          |

Study (CASS), surgical mortality decreased with increased patient height and coronary artery lumen diameter (which were correlated). Narrower coronary arteries may predispose short women to an increased risk for an obstructive thrombus. This of course would not explain why shorter men in our population do not demonstrate increased risk. We did not examine two potential confounders of the height-myocardial risk relation in women. First, although we adjusted for total cholesterol, it was not possible to adjust for high-density lipoprotein cholesterol, which was not available at the time of the index examination (1951 through 1955). Second, our study did not examine menopausal status or height loss after menopause as potential confounding variables. Further investigation will be needed to elucidate the relation between short stature in women and risk for myocardial infarction.

Our study has some advantages over other studies. Unlike the very early studies, the Framingham Heart Study offers longitudinal follow-up of a large population-based sample. This report is based on more than 35 years of follow-up, yielding a considerable number of outcome events, whereas the other prospective trials had fewer than 8 years of follow-up. We had the opportunity to study women as well as men, whereas all except one of the aforementioned studies examined only men. We examined all-cause mortality and cardiovascular disease mortality in addition to myocardial

infarction, whereas prior reports only examined coronary heart disease events or mortality. Last, unlike prior studies, we accounted for risk factor changes over time.

In summary, in our population, age appears to explain observed differences in mortality between shorter and taller individuals. We did not find an increase in myocardial infarction risk in shorter men, a departure from previous well-designed studies.<sup>4,5</sup> There was an increase in risk of myocardial infarction in shorter women.

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