Higher Risk of Cardiovascular Mortality Among Lean Hypertensive Individuals in Tecumseh, Michigan

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**Background** A cohort of 2181 men and women, aged 40 to 79 years, without evidence of coronary heart disease or cancer at entry to the Tecumseh Study was evaluated.

**Methods and Results** Subjects were defined as lean if their Metropolitan Life Insurance table relative weight was <110 (n=584) and as obese if their relative weight was ≥120 (n=1024). There were 688 subjects with hypertension at study entry (systolic blood pressure ≥160, diastolic blood pressure ≥95, or treated). The 29-year relative risk (RR) of mortality from ischemic heart disease (IHD) or cardiovascular disease (CVD) associated with systolic blood pressure level was significant for both lean and obese subjects. Among hypertensive subjects, the RR of fatal IHD for lean versus obese hypertensive subjects was 1.87 (95% confidence interval, 1.21 to 2.88) and the RR of fatal CVD was 1.56 (95% confidence interval, 1.10 to 2.20) using a Cox proportional-hazards model to adjust for the independent effects of age and traditional CVD risk factors. The findings are consistent with other studies in men showing lean hypertensive subjects to be at greater risk of IHD or CVD mortality than obese hypertensive subjects. A similar finding is now observed in women.

**Conclusions** Associations do not prove causality or dictate management. Nevertheless, the unexplained higher mortality in lean versus obese hypertensive subjects has now been reported with sufficient frequency to suggest that the association is real (if unexplained). Determining the reasons for this association may improve targeted prevention and treatment strategies. *(Circulation. 1994;89:703-711.)*

**Key Words** - follow-up studies - hypertension - obesity

A positive association between obesity or body weight and hypertension has been well established.1-3 Longitudinal studies have shown that weight gain is associated with a higher probability of becoming hypertensive.4-6 In addition, weight reduction among overweight hypertensive subjects usually results in a lowering of blood pressure.7 Hypertension itself is an established potent risk factor for cardiovascular disease.8 Although the impact of hypertension and obesity on cardiovascular disease (CVD) is a commonly accepted tenet, the independent role of obesity as a cause of a CVD event is more controversial.9-11 Furthermore, several prospective studies have reported excess ischemic heart disease (IHD) or CVD mortality among lean hypertensive subjects.12-16 This has led to considerable discussion regarding the relation between hypertension, body size, and cardiovascular disease.17-22 Because the Tecumseh Community Health Study helped to establish current concepts regarding hypertension, obesity, and cardiovascular disease,5,6,8,23 it was our aim to use the same data to reexamine the question of whether lean hypertensive subjects, both male and female, are at greater risk of fatal cardiovascular disease than obese hypertensive subjects.

**Methods**

The Tecumseh Study is a longitudinal investigation being conducted in a geographically defined area consisting of the midwestern town of Tecumseh, Michigan, and the rural area surrounding it.24,25 The study, which began in 1959, screened more than 88% of the community inhabitants during the first assessment period and continues to have approximately 80% participation at subsequent contacts.

Tecumseh participants have been followed from entry through 1987, a maximum of 29 years. The most recent ascertainment of vital status was complete for more than 99% of the cohort. Death certificates, which have been obtained for virtually all deaths, were coded using the ninth revision of the International Classification of Diseases (ICD).26Deaths were attributed to CVD based on ICD codes 401 to 448 and to ischemic heart disease based on ICD codes 410 to 414 or 429.2.

The entry evaluation included a medical history, physical examination, and laboratory measurements.27,28 Subjects were measured for height and weight in indoor clothing without shoes. Blood pressure was obtained from seated subjects by the attending physician using a standard mercury manometer. Subjects were identified as hypertensive if they had a systolic blood pressure ≥160 mm Hg, a diastolic blood pressure ≥95 mm Hg, or were using antihypertensive medication.

Serum cholesterol determinations were obtained from a casual blood sample analyzed by the Abell-Kendall laboratory method. The method was standardized using a recrystallized cholesterol standard.29 Individuals were classified as diabetic if they reported that they had been diagnosed as diabetic by their physician and had been treated with insulin or oral hypoglycemic agents. Untreated subjects were assigned to normal or elevated blood glucose categories on the basis of published

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Tecumseh criteria that considered glucose levels and test conditions. Those subjects diagnosed with diabetes and those with elevated levels of blood glucose were considered to have atypical glucose tolerance.

A Metropolitan Life Insurance relative weight index (MRW) that represents measured weight as a percentage of ideal weight for measured height was calculated for each subject. The ideal weights used were the midpoints of the sex-specific ranges of ideal weights for height determined as part of the 1959 Society of Actuaries’ Build and Blood Pressure Study. Subjects were categorized into five groups based on levels of MRW: <100% of ideal, 0% to 9% over ideal, 10% to 19% over ideal, 20% to 29% over ideal, and >30% over ideal. In turn, these groups were condensed into three categories: those <10% over ideal, those 10% to 19% over ideal, and those >20% over ideal. Two sets of comparisons were conducted contrasting the mortality experience of the leanest group (baseline weight <100% of ideal weight) with those ≥30% over ideal, and contrasting those whose weights were <10% over ideal with those whose weights were ≥20% over ideal. Those categorized as being <10% over their ideal weight had body mass indices ranging from 18.3 to 24.3 for men and 16.6 to 22.7 for women, whereas subjects who were categorized as >20% over ideal weight had body mass indices ranging from 26.5 to 43.9 for men and 24.7 to 56.5 for women. The median MRW for the hypertensive subjects in this cohort was 121.1 for men and 135.5 for women. Nearly 60% of hypertensive women and 33.7% of hypertensive men were >30% over their ideal weight.

Information regarding past and present smoking and alcohol habits was collected by trained interviewers. Alcohol consumption was ascertained from questions regarding use of alcohol, which included information concerning the types of alcoholic beverages consumed, the frequency of use, and the usual amounts consumed per occasion by beverage type. Current ethanol intake is reported as ounces of ethanol consumed per week and was estimated from baseline reports of frequency and usual amounts consumed. Past drinkers provided similar information regarding past usual frequency and amounts.

The present analyses were restricted to individuals, ages 40 to 79 years at entry, who were without evidence of coronary heart disease as determined by ECG findings or physician diagnosis at entry examination. Data were available from a study of the prevalence of cancer in the Tecumseh cohort that allowed the determination of subjects with pathologically confirmed cancers. Those subjects with cancer diagnosed before entry or within 2 years after entry were excluded from these analyses. Although there were 887 hypertensive subjects in the Tecumseh cohort, 171 were excluded from these analyses because of existing coronary heart disease at entry to the study, and 16 were excluded because they had pathologically diagnosed cancer. In addition, 4 subjects were excluded because of missing heights or weights, and 8 were lost to follow-up, leaving 688 hypertensive subjects for study.

Prevalence and mortality rates were adjusted for age using the direct method of age adjustment and eight 5-year age categories. Confidence intervals (CIs) for mortality rates were calculated assuming that the variance of the standardized rate is the sum of the weighted variances in each age category. The significance of differences in proportions for categorical variables was determined by χ² analyses with adjustments for age carried out by the Mantel-Haenszel method. Means of continuous variables were adjusted for age using ANCOVA.

The Cox proportional hazards model was used to analyze survival data for which the time to all-cause mortality, cardiovascular mortality, or IHD mortality might have been influenced by a set of one or more risk factors or covariates. Adjustments for smoking included both the current number of cigarettes smoked per day and a variable for smoking status (ever, never). Models that included adjustment for drinking also used variables for both drinking status (ever, never) and amounts consumed. Use of this multivariate technique allowed the independent relative risk (RR) associated with a prognostic variable to be evaluated while simultaneously adjusting for other baseline characteristics using progressively censored data. Length of follow-up for each subject was calculated by subtracting a subject’s date of entry into the study from their date of last contact, if they were alive at follow-up, or from their date of death.

### Results

#### Total Population

A total of 2181 men and women, aged 40 to 79 years, were free of both coronary disease and cancer at entry between 1959 and 1965; 32% were hypertensive. During the 29-year follow-up period, from entry through 1987, there were 455 deaths among persons classified as hypertensive at baseline. These 455 deaths included 151 IHD deaths, 105 additional CVD deaths, and 199 non-CVD deaths.

Table 1 shows the RR for IHD for age, sex, and systolic blood pressure in three relative weight categories, simultaneously adjusted for serum cholesterol, cigarette smoking status, atypical glucose tolerance, and use of antihypertensive medication. In these models, systolic blood pressure was a significant independent predictor of IHD death for all subjects, whether lean, intermediate weight, or obese.

The Figure compares the age-adjusted CVD mortality rates of the 688 hypertensive subjects with the remainder of the cohort, plotted by decile of MRW. Those with hypertension had higher CVD mortality rates than those without hypertension. The CVD mortality rates were higher in the middle and lower MRW categories than in the upper MRW categories, especially in women. The highest MRW categories had the lowest CVD mortality rates, with a sharp decline in risk in the upper MRW categories.
rates than normotensive subjects over the entire range of relative weight. The distance between the two curves is wider at lower levels of MRW and narrows by the sixth decile, suggesting a higher RR in lean hypertensive subjects than among obese hypertensive subjects. A similar pattern was observed for IHD deaths (data not shown).

**Hypertensive Subgroup**

Because our primary aim was to evaluate the association of relative weight with outcome among hypertensive subjects, the remainder of the analyses were restricted to the 688 men and women with hypertension. Table 2 shows the age-adjusted prevalence of selected cardiovascular risk factors among these hypertensive subjects over categories of relative weight. A significantly greater percentage of lean hypertensive subjects was male (61.9%) compared with obese hypertensive subjects (34.9%). Lean hypertensive subjects were more often current smokers at baseline (55.7%) than obese hypertensive subjects (27.9%). Lean subjects were more often current drinkers (68.1%) than obese hypertensive subjects (47.8%). Although not statistically significant, lean hypertensive subjects more often had ECG evidence of left ventricular hypertrophy (7.1%) than was exhibited by obese hypertensive subjects (4.4%). However, a greater percentage of obese hypertensive subjects had atypical glucose tolerance (14.9% versus 10.2%) and were taking antihypertensive medication compared with lean hypertensive subjects (16.4% versus 11.5%), although neither difference was statistically significant.

Table 3 shows a comparison of the age-adjusted means of selected cardiovascular risk factors measured as continuous variables by categories of MRW. A statistical comparison of the mean values for lean hypertensive versus obese hypertensive subjects found significant differences between the two categories for all examined risk variables except serum cholesterol and mean per-week ethanol consumption among current drinkers. Lean hypertensive subjects were older and had significantly lower blood pressures than subjects who were obese. They also had significantly smaller skinfolds, lower ratios of subscapular-to-triceps skinfolds, and they smoked more. Among the subset with postchallenge blood glucose levels, lean hypertensive subjects also had significantly lower blood glucose levels.

Table 4 presents sex-specific age-adjusted 29-year mortality rates from selected causes of death for three categories of MRW. This table shows that the age-adjusted death rate for all causes combined may be U-shaped, and that, for the subsets of all cardiovascular deaths or IHD deaths, there may be a higher proportion of deaths in the leanest of the three relative weight categories compared with the heaviest category. This pattern does not appear to hold for the broad category of non-CVD death, where rates in the leanest category

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**Table 2. Age-Adjusted* Baseline Prevalence Rates of Selected Cardiovascular Risk Factors Among 688 Hypertensive Subjects Over Three Categories of Relative Weight**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Lean MRW &lt;110 (n=110)</th>
<th>Moderate MRW 110-119 (n=125)</th>
<th>Obese MRW ≥120 (n=453)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>61.9</td>
<td>57.4</td>
<td>34.5†</td>
</tr>
<tr>
<td>Smoker, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>55.7</td>
<td>42.9</td>
<td>27.9†</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>10.7</td>
<td>20.5</td>
<td>15.7</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>33.6</td>
<td>36.6</td>
<td>56.4†</td>
</tr>
<tr>
<td>Drinker, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>68.1</td>
<td>52.2</td>
<td>47.8†</td>
</tr>
<tr>
<td>Ex-drinker</td>
<td>10.1</td>
<td>14.7</td>
<td>10.7</td>
</tr>
<tr>
<td>Never-drinker</td>
<td>21.8</td>
<td>33.1</td>
<td>41.5†</td>
</tr>
<tr>
<td>With left ventricular hypertrophy, %</td>
<td>7.1</td>
<td>5.1</td>
<td>4.4</td>
</tr>
<tr>
<td>With atypical glucose tolerance, %</td>
<td>10.2</td>
<td>19.5</td>
<td>14.9</td>
</tr>
<tr>
<td>Treated for hypertension, %</td>
<td>11.5</td>
<td>13.0</td>
<td>16.4</td>
</tr>
</tbody>
</table>

MRW indicates relative weight based on Metropolitan Life Insurance ideal weight tables.

*Percentages adjusted for age by the direct method of standardization.

†P < .05, comparison of lean vs obese using Mantel-Haenszel analysis.
are not significantly higher than those in the heaviest category. Indeed, for males, the non-CVD mortality rates in the leanest category are significantly lower than rates in the heaviest category. A further breakdown of non-CVD mortality into cancer and noncancer mortality revealed a trend toward increasing cancer mortality with increasing relative weight for both men and women. However, for other non-CVD deaths, where

| TABLE 3. Mean Age-Adjusted Baseline Values of Selected Cardiovascular Risk Factors Among 688 Hypertensive Subjects Over Three Categories of Relative Weight |
|-----------------|-----------------|-----------------|
| Risk Factor     | Lean MRW <110 (n=110) Mean (SE) | Moderate MRW 110-119 (n=125) Mean (SE) | Obese MRW ≥120 (n=453) Mean (SE) |
| Age, y*         | 57.3 (11.6) | 54.7 (9.2) | 55.2 (9.8) |
| Blood pressure  |                  |                  |                  |
| Systolic*       | 164.7 (1.9) | 163.6 (1.8) | 169.0 (0.9) |
| Diastolic*      | 94.2 (1.3)  | 95.2 (1.1)  | 99.0 (0.6)  |
| Skinfolds, mm   |                  |                  |                  |
| Subscapular*    | 12.7 (0.8)  | 17.2 (0.8)  | 28.8 (0.4)  |
| Triceps*        | 13.3 (0.7)  | 17.2 (0.7)  | 24.2 (0.4)  |
| Ratio*          | 1.0 (0.04)  | 1.1 (0.04)  | 1.3 (0.02)  |
| Serum cholesterol, mg/dL | 232.6 (4.3) | 237.0 (4.1) | 239.0 (2.2) |
| 1-Hour challenged glucose, mg/dL*† | 153.6 (6.1) | 171.6 (5.8) | 167.5 (3.0) |
| Cigarettes per day among smokers*† | 24.1 (1.8)  | 21.6 (1.8)  | 19.0 (1.2)  |
| Ethanol (oz/wk) among drinkers† | 4.1 (0.6)   | 3.3 (0.6)   | 3.3 (0.4)   |

MRW indicates relative weight based on Metropolitan Life Insurance ideal weight tables; SE, standard error.
*P<.05, comparison of lean vs obese adjusted for age using ANCOVA.
†n reduced for glucose to 77, 84, 310; n reduced for smokers to 58, 54, 124; n reduced for drinkers to 69, 66, 214.

| TABLE 4. Age-Adjusted Mortality Rates per 100 Persons for Selected Causes of Death by Sex and Categories of Metropolitan Relative Weight Among 688 Hypertensive Subjects |
|-----------------|-----------------|-----------------|
| MRW Category    | Deaths | Men Adjusted Rate (SE) | 95% Cl | Deaths | Women Adjusted Rate (SE) | 95% Cl |
| All deaths      |        |                  |        |        |                  |        |
| <110            | 55     | 75.8 (4.8)       | 66.3-85.2 | 30     | 72.1 (5.1)       | 62.0-82.2 |
| 110-119         | 52     | 69.6 (4.6)       | 60.6-78.6 | 29     | 54.6 (6.0)       | 42.8-66.3 |
| ≥120            | 107    | 73.6 (3.0)       | 67.7-79.5 | 178    | 57.3 (2.6)       | 52.3-62.4 |
| CVD deaths      |        |                  |        |        |                  |        |
| <110            | 38     | 48.0 (5.8)       | 36.6-59.3 | 20     | 44.5 (6.0)       | 32.8-56.1 |
| 110-119         | 33     | 44.6 (5.4)       | 34.0-55.2 | 16     | 27.2 (4.4)       | 18.5-35.8 |
| ≥120            | 48     | 37.5 (3.5)       | 30.6-44.4 | 98     | 31.5 (2.5)       | 26.6-36.4 |
| IHD deaths      |        |                  |        |        |                  |        |
| <110            | 24     | 31.2 (5.3)       | 20.9-41.5 | 13     | 29.8 (6.1)       | 18.0-41.7 |
| 110-119         | 23     | 31.2 (5.1)       | 21.3-41.1 | 8      | 13.9 (4.3)       | 5.5-22.3 |
| ≥120            | 28     | 20.7 (3.6)       | 13.8-27.7 | 53     | 17.3 (2.1)       | 13.2-21.5 |
| Non-CVD deaths  |        |                  |        |        |                  |        |
| <110            | 17     | 27.8 (5.2)       | 17.5-38.0 | 10     | 27.6 (5.9)       | 16.0-39.2 |
| 110-119         | 19     | 25.0 (4.9)       | 15.4-34.6 | 13     | 27.4 (5.1)       | 17.3-37.5 |
| ≥120            | 59     | 36.1 (3.8)       | 28.7-43.6 | 80     | 25.8 (2.5)       | 20.9-30.8 |

MRW indicates relative weight based on Metropolitan Life Insurance ideal weight tables; SE, standard error; CI, confidence interval; CVD, cardiovascular disease; and IHD, ischemic heart disease.
Sample sizes for men were MRW <110, 69; MRW 110-119, 73; MRW ≥120, 158; for women, MRW <110, 41; MRW 110-119, 52; and MRW ≥120, 295.
numbers were small and specific causes of death varied, no consistent pattern could be demonstrated.

We used Cox proportional-hazards models to evaluate the independent RR of both IHD mortality and CVD mortality associated with being lean compared with being obese. These models simultaneously adjusted for age, sex, systolic blood pressure, serum cholesterol, smoking status, cigarettes per day, atypical glucose tolerance, and use of antihypertensive medication. Table 5 shows the RRs for four selected causes of death that were associated with categories of relative weight. The RR of IHD mortality for the lean hypertensive subject with a MRW <110 versus the obese hypertensive subjects with a MRW ≥120 was significantly increased at 1.87 with a 95% CI of 1.21 to 2.88. When the same comparison was made for the leanest hypertensive subjects (MRW <100) versus the most obese category (MRW ≥130), the RR increased to 2.69 (95% CI, 1.50 to 4.83). The pattern of excess risk was similar for CVD mortality, but the risk was lower with an RR of 1.56 (95% CI, 1.10 to 2.20) for lean versus obese and of 1.86 (95% CI, 1.16 to 2.98) for leanest versus most obese subjects. Similar analyses were conducted that did not include systolic blood pressure as one of the risk factors in the Cox models. This resulted in similar RRs with significant results for the same event—relative weight comparison groups.

Sex-specific analyses were also conducted in an attempt to determine whether the pattern of excess risk of CVD or IHD mortality among lean hypertensive subjects was consistent for each sex. For women, the results were statistically significant and the RRs were similar in the group as a whole (Table 5). For men, the pattern of excess risk was similar although the RRs were lower and reached statistical significance at the \( \alpha = 0.05 \) level for the IHD end point only.

Because tobacco use is undoubtedly an important confounder in the association between CVD mortality and hypertension in lean subjects, separate analyses were repeated for smokers and nonsmokers (Table 6). We found that among male hypertensive smokers, the RR of IHD mortality associated with being <10% over ideal weight versus being ≥20% over ideal weight was 2.58 (95% CI, 1.07 to 6.24). There was also a significant excess risk for lean versus obese female hypertensive smokers. Among nonsmokers (never-smokers and ex-smokers) the RR for CVD mortality associated with being lean compared with being obese was significant for both sexes combined. However, in sex-specific analyses, although the RRs were greater than one, they achieved statistical significance only for CVD mortality among women. The 13 lean hypertensive men who had never smoked represent 4.3% of the hypertensive men and 6.7% of the CVD deaths in that group. The 28 lean hypertensive women who had never smoked represent 7.2% of hypertensive women and 9.7% of the CVD deaths. The small numbers of lean male never-smokers resulted in unstable mortality rates and precluded anal-
yses of RRs among male never-smokers. However, for never-smoking females, the RRs for being <10% over ideal weight compared with being ≥20% over ideal weight were 2.01 (95% CI, 0.86 to 4.70) for IHD and 2.22 (95% CI, 1.16 to 4.26) for CVD.

Among current drinkers, there was no significant difference in age-adjusted mean consumption of ethanol between categories of MRW, nor was there a significantly different proportion of past drinkers between these categories. However, the proportion of never-drinkers increased with increasing relative weight, especially for women. In results not shown, we tested Cox proportional-hazards models that included variables for alcohol-use status and ounces of ethanol consumed per week along with the other risk variables previously tested. Inclusion of these alcohol variables lowered RRs slightly but did not alter the direction or the significance of the excess CVD mortality risk observed among the lean hypertensive group.

**Discussion**

Consistent with other studies, we found that elevated blood pressure was associated with increased risk for CVD and IHD mortality in both obese and lean subjects, even after adjustment for confounders including smoking. Although this evidence continues to support the concept that elevated blood pressure is detrimental to health, the joint relation between body size and blood pressure on mortality experience remains controversial.

We observed that the relation between our measure of obesity and IHD or CVD mortality was not linear over the entire range of blood pressure. Indeed, we observed excess risk of mortality among lean hypertensive compared with obese hypertensive subjects. Graphic representations of measures of body mass and IHD or CVD mortality for several other cohort populations indicate, at least for hypertensive subjects, that the relation of body size and IHD or CVD mortality is not linear.\(^{12,14,17}\) It has been argued that failure to find a significant nonzero interaction between blood pressure and body size over the entire range of blood pressure must lead to the conclusion that lean hypertensive subjects are not at higher risk than those who are obese.\(^{17}\) We did fail to find a significant interaction between blood pressure and MRW for either IHD or CVD mortality when we assumed a linear relation over the entire blood pressure range. However, when we assumed a U-shaped or parabolic relation, we were able to demonstrate a significant interaction between body size and blood pressure for IHD mortality, although not for the more inclusive end point of all CVD mortality. If death rates from IHD or CVD for normotensive subjects increase with body size, findings for models that make no distinction between hypertensive and normotensive subjects may be distorted.\(^{16}\)

A clearer picture emerged in examining data from hypertensive subjects alone that supported the contention that lean hypertensive men and women are at greater risk of cardiovascular mortality than those who...
are obese. Issues that may confound these results include the distribution of smoking and alcohol use in the population and the presence of preexisting disease.

The role of smoking in the excess risk of lean hypertensive subjects for CVD mortality is of substantial interest, particularly because smoking is a risk factor that can be altered. Survival analyses, which adjusted for both smoking status and the number of cigarettes currently smoked per day, resulted in significant RR ratios for lean hypertensive subjects despite the adjustments for baseline smoking. When we examined the body size–mortality relation among current smokers, we found that the excess mortality for lean hypertensive subjects persisted. Analyses among nonsmokers also provided evidence for the excess risk. These nonsmokers do include past smokers whose risk may well be more like that of current smokers than never-smokers. Unfortunately, our ability to investigate whether this relation remains consistent among never-smokers is hampered by small numbers. Whereas the excess risk persisted among female never-smokers, numbers were too small to evaluate the RR for men. At the baseline Tecumseh examinations, which predated present antismoking advice, only 23% of male hypertensive subjects were never-smokers, and only 4.3% of male hypertensives were lean never-smokers.

Data from the Hypertension Detection and Follow-up Program (HDFP) also have been used to examine the mortality experience of hypertensive subjects across classes of body mass. They reported excess total mortality among lean hypertensive subjects, including excess CVD mortality among lean hypertensive men. However, they indicated that this excess mortality was most notable for non-CVD deaths. In the Tecumseh cohort, the excess RR of mortality from all causes for lean versus obese hypertensive subjects was not significantly elevated, in contrast to the stronger significant increased risk for IHD mortality. Moreover, for non-CVD mortality, the relation was inconsistent between the sexes. Whereas being lean was associated with a significantly reduced risk for non-CVD mortality in men, this was not true for women. The failure of these non-CVD models to achieve significance for both sexes could be a function of lack of statistical power caused by the relatively small number of non-CVD events in this study. Likewise, the lack of consistency between the sexes could be a function of the levels of other contributing risk factors.

Evidence from the HDFP study implicates alcohol and smoking as contributing factors to excess risk among lean hypertensive subjects because of excess neoplastic or respiratory deaths, observed among lean hypertensive subjects who smoked, and excess cirrhotic and violent deaths. Whereas there was a significant difference in smoking behavior between lean and obese hypertensive subjects in Tecumseh, the percentage of current smokers and the amount they smoked was lower than in the HDFP study. Furthermore, there was no significant difference in mean age-adjusted weekly ethanol consumption between lean and obese hypertensive subjects for either sex. Heavy drinking was not common among these hypertensive subjects: 87% drank less than one drink per day, only 1.2% consumed more than two drinks per day, and no one averaged more than four drinks per day. Among this cohort of hypertensive subjects, there were no cirrhotic deaths, and the two death certificates that mentioned cirrhosis as being present were for obese subjects. Furthermore, with only 16 violent deaths among hypertensive subjects, no excess risk for violent death could be demonstrated among lean hypertensive subjects in this cohort. Levels of deleterious lifestyle activities may not have been high enough among lean hypertensive subjects in Tecumseh to cause an excess in non-CVD mortality. Despite this situation, excess IHD and CVD mortality persist in this group.

Clearly, there are differences between the Tecumseh and HDFP cohorts. The Tecumseh cohort was drawn from a white midwestern farming community. The participants in these analyses were born between 1879 and 1924 and had been followed for up to 29 years. Subjects with known cancer or coronary heart disease at baseline were excluded from these analyses. The HDFP cohort was drawn from a cross section of communities and was designed to include urban and lower socioeconomic groups. Participants in the HDFP cohort, which included 44% blacks, were born between 1904 and 1943 and were followed for 8.3 years. Subjects were included regardless of baseline cancer or coronary disease status. Although these two cohorts may have diverged on many parameters, including alcohol intake, smoking habits, and distribution of body size, it is more remarkable that, despite these differences, both studies have provided evidence that there is a significant health risk for lean hypertensive subjects.

It would be reasonable to postulate that the disadvantage for lean hypertensive subjects is due to preexisting disease. For this reason, we excluded from the cohort all subjects with coronary heart disease or cancer at entry. Also, in analyses not presented, we removed all people who died within 5 years after entry. Removal of these early deaths did not change the significance or the pattern of risk.

It has been hypothesized that lean hypertensive subjects may suffer from higher peripheral vascular resistance than those who are obese. Messerli suggested that lower vascular resistance associated with an increase in body size could well serve as the pathophysiological mechanism by which obesity exerts a protective effect on certain vascular beds and ultimately decreases the risk of both coronary artery and peripheral vascular disease. Unfortunately, early Tecumseh data do not allow direct measurement of vascular resistance, cardiac output, or kidney function and therefore cannot be used to examine this theory.

In an effort to test the hypothesis that lean hypertensive subjects have suffered end-organ damage, we examined ECG evidence of left ventricular hypertrophy. In this cohort, the prevalence of left ventricular hypertrophy was disproportionately high among lean hypertensive subjects at 7.1% versus 4.4% for obese hypertensive subjects. Left ventricular hypertrophy itself did not reach statistical significance as an independent predictor of IHD or CVD death, and exclusion of all subjects with left ventricular hypertrophy did not alter the significance or the pattern of risk. Lean hypertensive subjects remained at excess risk for IHD death compared with obese hypertensives. Inclusion of left ventricular hypertrophy in the multivariate models did not alter the RRs or their significance.
None of these hypotheses address whether differences in outcome for lean and obese hypertensive subjects reflect genetically different types of hypertension. Subjects who are hypertensive without being overweight may well carry stronger genetic determinants of CVD than obese hypertensive subjects; likewise, these may be subjects who carry high blood pressure genes that are associated with other undescribed coronary heart disease risk factors specific to the lean. Recent publications have provided increased evidence of a genetic component to essential hypertension, which might also be linked to body size. This is an area that certainly should be further evaluated. For example, in the Tecumseh cohort, there is a significant association between self-reported family history of heart disease and subsequent IHD death among lean but not among obese hypertensive subjects. When our model included an interaction term for family history of heart disease and body size, the RR for IHD comparing lean hypertensive subjects with a positive family history to obese hypertensive subjects with no family history was 2.20 (95% CI, 0.92 to 5.23). This result is suggestive but achieves significance only at the .08 level. Limitations in the sample size may be the reason for this wide CI; undertaking new studies or combining data from existing studies might more fully elucidate a genetic component in this relation.

All death certificates were reviewed for misclassification. The only obvious problem was the assignment of cause of death to diabetes for 16 obese hypertensive subjects whose immediate cause of death was a cardiovascular event. Analyses performed after these cases were recoded reduced the RR without a change in the significance of the association or the conclusion that lean hypertensive subjects are at higher risk.

An increased risk of cardiovascular mortality does not appear to be an artifact of inappropriate blood pressure measurement. Mean age-adjusted blood pressures were significantly lower among lean hypertensive subjects than among those who were obese. Lower IHD or CVD mortality rates among obese hypertensive subjects could be a result of inappropriate cuff size if the effect on measured blood pressure was sufficient to result in a misclassification from normotensive to hypertensive. Obese subjects with blood pressure readings within approximately 10 mm Hg of the systolic or diastolic cutoff points for hypertension may be at risk of misclassification. Although the earliest examinations did not use large cuffs for heavier subjects, we could not demonstrate that this resulted in significant misclassification. In this cohort, there were 55 hypertensive subjects who had arm circumferences ≥35 cm. Only 12 of these 55 had blood pressures low enough to present a misclassification problem. Exclusion of these 12 subjects did not affect the magnitude or the significance of the reported RRs. Exclusion of all 55 subjects with large arms actually increased the RRs reported for lean hypertensive subjects. Furthermore, inclusion of arm circumference into the Cox model did not affect the size or the significance of the reported RRs.

As with any longitudinal study, there are problems in trying to predict mortality using baseline risk factors that do not stay static over the length of the follow-up period. Changes in smoking habits, blood pressure control, type of antihypertensive medication, and even body weight all could have an influence on the mortality of these hypertensive subjects. The Tecumseh cohort has experienced a reduction in smoking and changes in treatment patterns for hypertension that parallel changes experienced throughout the United States during the last three decades. At baseline in 1959, 56% of the lean and 28% of the obese hypertensive subjects were current smokers. By 1978, the percentage of smokers had dropped to 32% of the lean and 16% of the obese. Although these smoking habit changes could have an effect on the differential mortality rates between lean and obese smokers, they do not explain why lean female never-smokers also experienced excess mortality in comparison with obese female never-smokers. Changes in treatment for hypertension may be more relevant. At baseline, only 10% to 15% of hypertensive subjects were treated with medication, and the medications used were often not effective. The difference in the proportion of lean versus obese subjects treated with antihypertensives was not statistically significant. However, by the end of the second decade of follow-up, treatment was much more widespread, and drugs were more efficacious. Information from a 1978 survey of the community shows that while the proportion of lean hypertensive subjects receiving antihypertensive therapy had risen to 47%, the proportion of obese subjects receiving similar therapy had risen to nearly 70%. It is reasonable to speculate that obese hypertensive subjects in this cohort were more likely to be placed under effective blood pressure control and more rigorously encouraged to quit smoking than their lean counterparts.

We have shown that lean hypertensive subjects, men and women, are at significantly higher risk for CVD mortality than obese hypertensive subjects. This excess risk was not eliminated by adjustments for age, sex, smoking status and cigarettes, serum cholesterol, atypical glucose parameters, use of antihypertensive medication, or the presence of preexisting left ventricular hypertrophy, coronary disease, or cancer. Other factors such as insulin resistance, central fat distribution, arrhythmias, kidney disease, or lack of appropriate treatment may provide clues to the cause of this excess risk. Unfortunately, the relatively small numbers of cause-specific deaths in each sex/weight/smoking group restrict the statistical power of this study to identify additional characteristics that are associated with this excess risk among lean hypertensive subjects. Further research may help to clarify whether hypertension in lean individuals is a distinct disease with strong genetic determinants or whether differences in outcome reflect increased vascular resistance.

The health risk to overweight individuals with hypertension is well documented. Being overweight is a risk factor for hypertension; hypertension, at any weight, is a significant risk factor for CVD mortality. Our results are consistent with this statement and should not be misinterpreted. These results do not suggest any diminution of the apparently causal role of obesity in hypertension. Furthermore, they do not imply that there should be any relaxation in the treatment of obese hypertensive individuals, whether that treatment is weight loss, dietary change, medication, or other therapy. However, the standard weight-loss advice given to overweight patients with hypertension is not likely to be appropriate for lean
hypertensive individuals. These analyses underscore the fact that those who are hypertensive, despite being lean, are at significantly increased risk for CVD mortality; determining the reasons for this risk may allow better targeted treatment and prevention strategies.

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