Hematocrit and the risk of coronary heart disease mortality

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Background An association between hematocrit (Hct) and coronary heart disease (CHD) mortality has been previously observed. However, the relationship of Hct and CHD independent of other cardiovascular disease (CVD) risk factors and differences between men and women remain unclear.

Methods We examined the association between Hct and CHD mortality with Cox regression analyses of data from 8896 adults, aged 30-75 years, in the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study (1976-1992). Covariates included age, sex, race, education, smoking status, hypertensive status, total serum cholesterol, body mass index, white blood cell count, and history of CVD and diabetes. Hct was categorized by use of sex-specific tertiles, and all analyses were stratified by sex.

Results During 16.8 years of follow-up, there were 545 (men 343, women 202) deaths from CHD (International Classification of Diseases, 9th revision [ICD-9] 410-414), 778 (men 426, women 279) deaths from diseases of the heart (ICD-9 390-398, 402, 404, 410-414, 415-417, 420-429), and 2046 (men 1216, women 830) all-cause deaths. Among men, the crude CHD mortality rate per 10,000 population was 42.6, 31.9, and 46.3 among those with Hct in the lower, middle, and upper tertiles, respectively. The corresponding crude CHD mortality rates among women were 12.6, 18.6, and 27.7. After adjustment for age and other CVD risk factors, there was no association between Hct in the upper tertile compared with the lower tertile and mortality from either CHD, diseases of the heart, or all causes among men. Women with Hct in the upper tertile were 1.3 times (95% CI 0.9–1.9) more likely to die from CHD than were women with Hct in the lowest tertile, after multivariate adjustment. The effect of high Hct on CHD mortality among women younger than 65 years of age was slightly stronger (relative risk 2.2, 95% CI 1.0–4.6).

Conclusions These results suggest that the association between Hct and mortality from CHD and all causes is complex, differing both by sex and age. Further research is needed to gain a better understanding of these age and sex differences. (Am Heart J 2001;142:657-63.)
stitionalized population of the United States aged 6 months to 74 years. A detailed description of the NHANES II survey and sampling procedures has been provided elsewhere.20

Briefly, data were collected through responses to questions on individual medical history, food consumption, and health-related behavior.20 In addition, persons underwent a physical examination by a physician. Hct (percent), WBCs (×10⁹ per liter) and red blood cells (RBCs) (×10¹² per liter), serum cholesterol (millimoles per liter), height (centimeters), weight (kilograms), and systolic blood pressure and diastolic blood pressure (millimeters of mercury) were measured. Hct was ascertained by the spun microhematocrit method.21 WBCs were performed on a Coulter counter (model FN). To obtain a more accurate measure of blood pressure, 3 blood pressure readings were recorded. The blood pressure used in this analysis was the mean value of the second and third readings. Hypertension was defined as a baseline systolic blood pressure ≥140 mm Hg or a baseline diastolic blood pressure ≥90 mm Hg or the current use of antihypertensive medication. Persons also completed a medical history that included questions about prior CVD and smoking history including lifetime smoking history (ie, smoked at least 100 cigarettes during lifetime) and current smoking status (Yes/No). Former smokers were identified as those who reported edly smoked at least 100 cigarettes during their lifetimes but who were not currently smoking.

Baseline data from NHANES II was merged with follow-up data from the NHANES II Mortality Study. As part of the NHANES II Mortality Study, data from the National Death Index, which captures 95% to 98% of all mortality,22-24 and from the Social Security Administration Death Master File were used to ascertain the vital status of each cohort member through December 31, 1992 (approximately 16.8 years of follow-up). Information obtained from the Mortality Study data includes the month and year in which an individual was last known to be alive and the International Classification of Disease, 9th revision (ICD-9), code for the underlying cause of death. Because only month and year of the date of death were ascertained, the 15th day of the month was analyzed as the day of the date last known to be alive for decedents. For all others, December 31, 1992, was assigned as the last known date alive. Follow-up (ie, survival) time was calculated as the difference between the NHANES II baseline examination date for each subject and the last known date alive obtained from the NHANES II Mortality Study.

Our analysis was limited to a subset of those persons aged 30 to 75 years who were followed up prospectively by the NHANES II Mortality Study. From the NHANES II Mortality Study cohort (n = 9250), we excluded persons with missing data for WBC count (n = 147); RBC count (n = 18); systolic blood pressure and diastolic blood pressure (n = 63); history of MI, heart failure, or stroke (n = 15); physical activity (n = 14); and educational attainment (n = 91). In addition, we excluded persons with a WBC count >19,000 cells/L (n = 6), which may indicate the presence of underlying acute illness or infection.

For the 8896 persons with complete information, a Cox proportional hazard regression model was used to assess the independent relationship between Hct and mortality from CHD, diseases of the heart, and all causes in age- and multivariate-adjusted analyses. CHD mortality was defined by ICD-9 codes 410-414 and diseases of the heart mortality by ICD-9 codes 390-398, 402, 404, 410-414, 415-417, and 420-429. Categories of Hct were defined by sex-specific tertiles. Crude mortality rates (per 10,000 population) for each cause of death were calculated by dividing the number of persons who died by the follow-up time for all persons. Relative risk estimates were obtained comparing persons in the middle and highest tertiles with those in the lowest tertile. Multivariate models were adjusted for age, race, sex, education, smoking status, hypertensive status, cholesterol level, body mass index (BMI), WBC count, and history of CVD and diabetes. Interaction terms composed of 2 dichotomous Hct variables and a dichotomous sex variable were included as well. We also examined whether smoking was an effect modifier of the association between Hct and mortality and found no evidence of interaction. In addition to modeling the categorical Hct, a continuous measure of Hct was entered in the final multivariate models for men and women. A 1-unit change in Hct corresponds to a 10-point change in Hct (eg, from Hct = 30% to Hct = 40%). To make the statistical estimates from the NHANES II data representative of what would have been obtained if the entire US population had been sampled, sample weights were used in all analyses. A χ² test was used to compare differences in categorical variables across groups, and analysis of variance was used to compare differences in continuous variables across sex-specific tertiles. P values were adjusted for multiple comparisons by means of the Bonferroni adjustment (P value ÷ number of comparisons) to ensure that the overall probability of a type I error was ≤0.05. To account for the complex sampling design and to achieve accurate variance estimates, we used SUDAAN 7.0 (Research Triangle Institute, 1996). All statistical inferences were based on a significance level of .05.

Results

The mean Hct for men (44.1, SE 0.07) and women (40.1, SE 0.08) differed significantly (P < .01), suggesting 2 different underlying distributions of Hct for the sex groups. Therefore baseline characteristics by Hct are shown in Table I separately for men and women. For both men and women, those with higher Hct were less likely to be African American and more likely to be hypertensive and current smokers. Among current smokers, the mean number of cigarettes increased with increasing Hct for men and women. Among women, but not men, those with a higher Hct were also more likely to have histories of MI and heart failure compared with those with a lower Hct. A history of diabetes was more prevalent among women with a higher Hct. Mean BMI, WBC count, and RBC count were significantly higher among men and women with Hct in the upper tertile compared with those with Hct in the lower tertile.

During 16.8 years of follow-up, there were 545 (men 343, women 202) deaths from CHD, 778 (men 426, women 279) deaths from diseases of the heart, and 2046 (men 1216, women 830) all-cause deaths. Sex was a significant modifier of the association between Hct and mortality. Among men, mortality from CHD and disease of the heart followed a J- or U-shaped pattern with increasing Hct (Figure 1), whereas crude mortality
rates increased across Hct tertiles among women (Figure 2). Similar relationships were observed for all-cause mortality for which the crude mortality rates were 150.9, 127.3, and 145.6 (per 10,000) among men in the lower, middle, and upper tertiles, respectively, and 74.0, 71.1, and 124.0 among women.

Table I. Characteristics of 4213 men and 4683 women by sex-specific tertiles of Hct: NHANES II Mortality Study

<table>
<thead>
<tr>
<th></th>
<th>Men Hct 19.0-43.0 (n = 1629)</th>
<th>Men Hct 43.2-45.2 (n = 1220)</th>
<th>Men Hct 45.5-61.7 (n = 1364)</th>
<th>Women Hct 14.5-39.0 (n = 1706)</th>
<th>Women Hct 39.2-41.5 (n = 1528)</th>
<th>Women Hct 41.7-58.5 (n = 1449)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American (%)</td>
<td>12.9</td>
<td>6.3</td>
<td>6.6*</td>
<td>15.1</td>
<td>8.4</td>
<td>4.3*</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>49.8 (0.35)</td>
<td>48.2 (0.35)†</td>
<td>48.7 (0.45)</td>
<td>47.8 (0.37)</td>
<td>49.6 (0.44)†</td>
<td>51.5 (0.42)†</td>
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<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 y</td>
<td>35.4</td>
<td>32.4</td>
<td>34.4</td>
<td>35.3</td>
<td>32.5</td>
<td>37.1</td>
</tr>
<tr>
<td>12 y</td>
<td>30.3</td>
<td>30.7</td>
<td>32.8</td>
<td>38.9</td>
<td>42.1</td>
<td>38.3</td>
</tr>
<tr>
<td>&gt;12 y</td>
<td>34.3</td>
<td>36.9</td>
<td>32.9</td>
<td>25.8</td>
<td>25.4</td>
<td>24.6</td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>8.7</td>
<td>10.4</td>
<td>10.1</td>
<td>10.1</td>
<td>9.2</td>
<td>13.9*</td>
</tr>
<tr>
<td>Moderately active</td>
<td>77.9</td>
<td>77.2</td>
<td>79.6</td>
<td>81.5</td>
<td>82.6</td>
<td>79.0</td>
</tr>
<tr>
<td>Very active</td>
<td>13.4</td>
<td>12.5</td>
<td>10.3</td>
<td>8.4</td>
<td>8.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Hypertensive (%)§</td>
<td>48.3</td>
<td>48.0</td>
<td>57.6*</td>
<td>37.9</td>
<td>44.7</td>
<td>51.9*</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>30.2</td>
<td>38.3</td>
<td>51.4*</td>
<td>22.2</td>
<td>30.3</td>
<td>47.9*</td>
</tr>
<tr>
<td>Former smoker (%)</td>
<td>41.9</td>
<td>35.4</td>
<td>29.8*</td>
<td>18.3</td>
<td>17.8</td>
<td>13.4*</td>
</tr>
<tr>
<td>Mean No. of cigarettes/d</td>
<td>6.6 (0.30)</td>
<td>9.1 (0.51)†</td>
<td>13.6 (0.62)†</td>
<td>3.7 (0.28)</td>
<td>5.5 (0.38)†</td>
<td>10.6 (0.54)†</td>
</tr>
<tr>
<td>Mean cholesterol (mmol/L)</td>
<td>5.6 (0.04)</td>
<td>5.7 (0.04)§</td>
<td>5.8 (0.05)§</td>
<td>5.7 (0.04)</td>
<td>5.8 (0.04)§</td>
<td>6.1 (0.05)§</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>25.5 (0.13)</td>
<td>25.9 (0.12)</td>
<td>26.5 (0.12)§</td>
<td>25.1 (0.15)</td>
<td>25.8 (0.14)</td>
<td>26.7 (0.27)§</td>
</tr>
<tr>
<td>Mean WBCs (×10⁹ cells/L)</td>
<td>6.8 (0.08)</td>
<td>7.3 (0.08)§</td>
<td>8.0 (0.10)§</td>
<td>6.4 (0.06)</td>
<td>7.0 (0.07)</td>
<td>7.7 (0.09)§</td>
</tr>
<tr>
<td>Mean RBCs (×10¹² cells/L)</td>
<td>46.4 (0.15)</td>
<td>49.4 (0.16)†</td>
<td>52.3 (0.16)†</td>
<td>41.8 (0.13)</td>
<td>44.9 (0.15)†</td>
<td>47.9 (0.18)†</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>6.8</td>
<td>4.6</td>
<td>5.4</td>
<td>2.5</td>
<td>1.8</td>
<td>3.9*</td>
</tr>
<tr>
<td>History of heart failure (%)</td>
<td>2.0</td>
<td>0.8</td>
<td>1.4</td>
<td>0.7</td>
<td>0.4</td>
<td>1.8*</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>1.8</td>
<td>1.9</td>
<td>2.0</td>
<td>1.7</td>
<td>1.7</td>
<td>2.2</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>4.7</td>
<td>2.5</td>
<td>4.0*</td>
<td>4.1</td>
<td>4.1</td>
<td>6.3*</td>
</tr>
</tbody>
</table>

SEs reported in parentheses.
*Statistically significant difference in variable proportions across hematocrit categories within sex group, P < .05.
†Statistically significant difference in variable means between hematocrit tertiles 1 and 2 within sex group, P < .05.
‡Statistically significant difference in variable means between hematocrit tertiles 1 and 3 within sex group, P < .05.
§Hypertensive at baseline defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg, or the current use of antihypertensive medication.
§§Statistically significant difference in variable means between hematocrit tertiles 2 and 3 within sex group, P < .05.
After adjustment for age and other CVD risk factors, there was no association between Hct in the upper tertile compared with the lower tertile and mortality from either CHD, diseases of the heart, or all causes among men (Table II), and these results did not differ by age group (<65 vs ≥65 years). Women with an Hct in the upper tertile were 1.3 times (95% CI 0.9–2.0) more likely to die from CHD than were women with an Hct in the lowest tertile after multivariate adjustment (Table III). A slightly stronger effect of high Hct on CHD mortality was observed among women younger than 65 years old after adjustment for CVD risk factors (relative risk [RR] 2.2, 95% CI 1.0-4.6), although the confidence interval is wide because of relatively few deaths (n = 67). No association was observed between CHD mortality and Hct in the upper tertile compared with the lowest tertile among women aged 65 years and older (RR 1.0, 95% CI 0.7–1.6).

Similar results were observed for diseases of the heart mortality. Women younger than 65 years old with an Hct in the upper tertile were twice (95% CI 1.2-3.4) as likely to die from diseases of the heart than women with Hct in the lowest tertile, as were women younger than 65 years old with Hct in the middle tertile (RR 2.0, 95% CI 0.9-4.3). Again, no association was observed between Hct and diseases of the heart mortality among women aged 65 years and older. For all-cause mortality, women aged <65 years in the upper tertile had a modestly increased risk of mortality (RR 1.1, 95% CI 0.8-1.6) compared with women in the lowest tertile, whereas women in the middle tertile were at slightly decreased risk (RR 0.8, 95% CI 0.5-1.2). Neither of these estimates attained statistical significance. For women aged ≥65 years, those with an Hct in the upper (RR 0.9, 95% CI 0.7-1.1) and middle (RR 0.7, 95% CI 0.6-0.9) tertiles were at decreased risk of all-cause mortality compared with women in the lowest tertile after multivariate adjustment.

In addition to the above analyses where Hct was categorized into sex-specific tertiles, we entered a continuous measure of Hct into the final multivariate-adjusted model for men and women. A 1-unit change was scaled...
to represent a 10-point change in Hct (eg, from 30% to 40%). A 10-point increase in Hct was associated with a 70% ($P = .17$) increased risk of CHD mortality among women and a 20% ($P = .30$) decreased risk among men after adjustment for other CVD risk factors, although neither of the point estimates attained statistical significance. Similar results were observed for diseases of the heart.

**Discussion**

Consistent with the findings of previous studies, our results indicate that elevated Hct is associated with several CVD risk factors, including cigarette smoking, blood pressure, and total cholesterol. In addition, the association between Hct and mortality is different for men and women. Crude mortality rates among men suggest a nonlinear relationship between Hct and mortality from CHD, diseases of the heart, and all causes; however, these associations were not apparent after adjustment for CVD risk factors. Crude mortality rates among women suggest a linear relationship between Hct and mortality from CHD and diseases of the heart and a J-shaped relationship for all-cause mortality. After stratification on age, we observed that a high Hct among younger women was associated with increased risk of CHD and diseases of the heart mortality. In contrast, Hct levels in the middle and upper terciles among older women were associated with a decreased risk of all-cause mortality after adjustment for CVD risk factors.

These findings are somewhat consistent with results from the Framingham Heart Study, where Gagnon et al observed a J- or U-shaped relationship between Hct and all-cause mortality independent of other CVD risk factors among men and women. A nonlinear relationship was also observed among women aged 35 to 64 years such that those with an Hct >45% or an Hct <40% were at significantly increased risk of CHD mortality compared with those with an Hct of 42% to 45% after adjustment for CVD risk factors. Gagnon et al also observed a significant positive association between high Hct (>48%) and risk of CVD mortality and a marginally significant association for CHD mortality among men aged 64 years and older relative to those with an Hct of 45% to 46%. Framingham men aged younger than 64 years with an Hct >48% were at decreased risk of CHD mortality relative to those with an Hct of 45% to 46%, but the estimates did not reach statistical significance.

Our results for men are inconsistent with those of Carter et al, Sorel et al, and Erikssen et al, which identified positive associations between elevated Hct and CHD mortality among men from Hawaii, Puerto Rico, and Norway, respectively. Among men of Japanese ancestry, age-adjusted CHD mortality rates increased with increasing Hct, although the association was not significant after adjustment for other CVD risk factors. Among men from Puerto Rico, a positive association was also observed between increasing Hct and CHD for those living in urban areas and those aged 55 to 64 years in rural areas. An overall decreasing trend was observed among those men aged 45 to 54 years from rural areas. A positive relationship between Hct and CHD and CVD mortality was also observed after 16 years of follow-up among a cohort of Norwegian men aged 40 to 59 years. After adjustment for age, smoking, systolic blood pressure, cholesterol, and erythrocyte sedimentation rate, Hct was associated with an increased risk of CVD mortality for 10 to 16 years of follow-up (RR 2.9 to 1.9). The contrasting results between our study and the previous 3 studies suggest that there may be differences among the populations that affect the observed association between Hct and CHD among men.

Gagnon et al note 3 plausible mechanisms for the Hct-CHD association: (1) increases in Hct may translate into increased blood viscosity, peripheral resistance, and decreased cardiac output; (2) the effect of elevated Hct may reflect a relationship with other CVD risk factors such as hypertension; and (3) increases in Hct may lead to atherosclerosis through RBC aggregation. Karino and Goldsmith found an increase in endothelial wall adhesion of platelets with increasing Hct, a finding that also suggests a role for atherogenesis and thrombosis. Animal models have shown that decreases in the Hct are associated with a lower arterial thrombosis rate and that normalization of the Hct results in the appearance of thrombosis. Carallo et al observed higher Hct among men with internal carotid atherosclerosis than among age-matched controls (48.6% vs 45.6%, $P < .01$). And, higher mean Hct values were found among men and women from the Edinburgh Artery Study who had intima-media thickness (IMT) <1.05 mm and 0.95 mm, respectively, compared with those with IMT <0.65 mm. Greater IMT has also been observed among smokers compared with nonsmokers.

It is possible that Hct serves as a marker for the effects of smoking on atherogenesis. Current smoking was strongly associated with high Hct for both men and women. However, our results suggest that Hct may be associated with mortality independent of smoking. There was no evidence of interaction between smoking and Hct, and inclusion of smoking in the final models attenuated the association between Hct and CHD as well diseases of the heart and all-cause mortality but did not fully explain away this association.

Although there is growing evidence of an association between elevated Hct and CHD independent of other CVD risk factors, the sex differences in the association between Hct and CHD mortality are not well understood. The manner in which such differences affect the
risk of CHD may be partly explained through the effects of estrogen on CVD. An association between estrogen and platelet aggregation has been observed, and Frohlich et al observed lower fibrinogen and plasma viscosity among women aged 52 to 65 years who were on hormone replacement therapy. Estrogen has also been found to affect blood vessel walls and smooth muscle cell proliferation. Finally, use of oral contraceptives, which has been associated with increased blood viscosity and fibrinogen, may also partly explain the observed association between Hct and CHD among younger women.

The results of this analysis are subject to several possible limitations. This analysis used a single Hct measurement to predict mortality. It is possible that multiple Hct measurements over time and changes in those measurements may provide a more accurate mechanism for studying the effect of blood viscosity on future disease and mortality. If so, it is possible that we have underestimated the effect of Hct on CHD mortality, and thus any observed association is likely a conservative one. It is also possible that the categorization process (ie, tertiles) for Hct resulted in some misclassification. However, we attempted to address this issue by entering a continuous Hct measure in the final multivariate models stratified by sex.

In conclusion, the results of this study suggest a non-linear relationship between Hct and all-cause mortality for men and women, although an association independent of other CVD risk factors remains unclear. The association between Hct and mortality from CHD and diseases of the heart differed by age and sex. We failed to identify an association between Hct level and CHD mortality independent of traditional CVD risk factors. Further research is needed to gain a better understanding of these sex differences.

References