Risk Factors for 5-Year Mortality in Older Adults

The Cardiovascular Health Study

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Context.—Multiple factors contribute to mortality in older adults, but the extent to which subclinical disease and other factors contribute independently to mortality risk is not known.

Objective.—To determine the disease, functional, and personal characteristics that jointly predict mortality in community-dwelling men and women aged 65 years or older.

Design.—Prospective population-based cohort study with 5 years of follow-up and a validation cohort of African Americans with 4.25-year follow-up.

Setting.—Four US communities.

Participants.—A total of 5201 and 685 men and women aged 65 years or older in the original and African American cohorts, respectively.

Main Outcome Measures.—Five-year mortality.

Results.—In the main cohort, 646 deaths (12%) occurred within 5 years. Using Cox proportional hazards models, 20 characteristics (of 78 assessed) were each significantly (P<.05) and independently associated with mortality: increasing age, male sex, income less than $50 000 per year, low weight, lack of moderate or vigorous exercise, smoking for more than 50 pack-years, high brachial (≥127 mm Hg) and low tibial (≥127 mm Hg) systolic blood pressure, diuretic use by those without hypertension or congestive heart failure, elevated fasting glucose level (>7.2 mmol/L [130 mg/dL]), low albumin level (≤37 g/L), elevated creatinine level (≥106 µmol/L [1.2 mg/dL]), low forced vital capacity (≤2.06 mL), aortic stenosis (moderate or severe) and abnormal left ventricular ejection fraction (by echocardiography), major electrocardiographic abnormality, stenosis of internal carotid artery (by ultrasound), congestive heart failure, difficulty in any instrumental activity of daily living, and low cognitive function by Digit Symbol Substitution test score. Neither high-density lipoprotein cholesterol nor low-density lipoprotein cholesterol was associated with mortality. After adjustment for other factors, the association between age and mortality diminished, but the reduction in mortality with female sex persisted. Finally, the risk of mortality was validated in the second cohort; quintiles of risk ranged from 2% to 39% and 0% to 26% for the 2 cohorts.

Conclusions.—Objective measures of subclinical disease and disease severity were independent and joint predictors of 5-year mortality in older adults, along with male sex, relative poverty, physical activity, smoking, indicators of frailty, and disability. Except for history of congestive heart failure, objective, quantitative measures of disease were better predictors of mortality than was clinical history of disease.

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A list of participants in the Cardiovascular Health Study Collaborative Research Group was published previously (J Am Geriatr Soc. 1997;45:1423-1433).

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Mortality in Older Adults—Fried et al

Participants were reinterviewed every 6 months. Confirmation of death was conducted through reviews of obituaries, medical records, death certificates, and the HCFA health care utilization database for hospitalizations. Through these methods, as well as interviews of contacts and proxies for participants unavailable for follow-up, there was 100% complete follow-up ascertainment of mortality status.

Analytic Methods

Study participants were followed up for an average of 4.8 years (range, 4.5-5.5 years). Mortality rates were calculated per 1000 person-years. Descriptive statistics are reported for the entire study population at baseline.

Characteristics hypothesized to be associated with mortality over 5 years were organized into related groups of variables, including risk factors for disease, subclinical measures of disease, clinical history of disease, and outcomes of disease. Characteristics selected are listed in Table 1 (column A and first footnote). Continuous variables were recoded into 5 intervals, chosen to have approximately the same number of deaths in each interval. This method of recoding is useful for identifying nonlinear effects of the variables and provides more stable relative risk (RR) estimates. Additionally, sex-specific quintiles were calculated for weight and height.

Unadjusted instantaneous hazard ratios (referred to as RRs throughout the article) were computed, first for descriptive purposes for each variable from a Cox model with only that 1 variable in the model (Table 1, column E). Then, sequential models were analyzed, in which all variables in group 1 (demographics) were allowed to enter in a stepwise Cox regression based on the $P$ value at each step (the $P$ for entry was .05 and for removal was .10). The next sequential Cox model began with the significant variables remaining from the previous model. Then, a new group of variables (group 2) was allowed to enter, using the stepwise entry procedure. Modeling proceeded in a similar manner for each successive group of variables. The results for these models were similar to those obtained when all variables were allowed to compete for entry (see next paragraph); these results are not displayed.

A final stepwise Cox model was computed allowing all variables that had previously been significant at any step to compete for entry. A missing value category was added to all variables with 1 or more missing values, except when the missing value was most likely attributable to lack of understanding of a question and it was very likely that the participant did not have the condition specified (eg, diabetes, CHF, coronary heart disease, or cerebrovascular disease), or a positive condition for the variable with the missing value was rare (eg, an abnormal ejection fraction). In the latter cases, the missing data were recoded as the normal condition. As the number of such missing data was quite uncommon in CHS for most variables, the recoding of the variables in this way had little effect on most of the parameter estimates. Models were tested using data only from participants with no missing data and, separately, based on the entire sample with missing data replaced as described above; the results with the imputed data were similar, but slightly more conservative and therefore are presented here (Table 1, column F). The RR of mortality was expressed for the categories of each
Table 1.—Association of Population Characteristics With 5-Year Mortality in 5201 Men and Women Aged 65 Years or Older: Unadjusted and Final Adjusted Models, the Cardiovascular Health Study

<table>
<thead>
<tr>
<th>Group 1: demographic and social factors</th>
<th>A Variable</th>
<th>B No. of Deaths</th>
<th>C No. at Risk</th>
<th>D Death Rate (per 1000 Person-Years)</th>
<th>E Unadjusted RR (95% CI)</th>
<th>P Value</th>
<th>F Final Model RR (95% CI)</th>
<th>P Value</th>
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<td></td>
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<tr>
<td>65-69</td>
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<td>70-74</td>
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<td>Sex</td>
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<td>2962</td>
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<td>2239</td>
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<td>1197</td>
<td>32.8</td>
<td>1.37 (1.15-1.63)</td>
<td></td>
<td>&lt;.001</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Group 2: anthropometric variables

| Weight, kg (lb)                          |            |                |              |                                        |                         |         |                          |         |
| ≤63.9                                   |            |                |              |                                        |                         |         |                          |         |
| >63.9-70.2 (142-156)                     |            |                |              |                                        |                         |         |                          |         |
| >70.2-77.4 (156-172)                     |            |                |              |                                        |                         |         |                          |         |
| >77.4-85.5 (172-190)                     |            |                |              |                                        |                         |         |                          |         |
| >85.5 (190)                              |            |                |              |                                        |                         |         |                          |         |

Group 3: lifestyle factors

| Physical activity, kJ (kcal)/wk in moderate or vigorous exercise | 282 (67.5) | 282-1789 (67.5-472.5) | 1789-4100 (472.5-980.0) | ≤1179 (980.0-1890.0) | 7908 (1890.0) |
| Pack-years smoking | 246 | 2358 | 21.7 | 1.00 |
| 1-25 | 124 | 1119 | 23.0 | 1.06 (0.85-1.32) |
| >25-50 | 127 | 952 | 28.0 | 1.29 (1.01-1.60) |
| >50 | 138 | 645 | 46.6 | 2.07 (1.65-2.58) |

Alcohol, drinks/d

| None | 351 | 2489 | 29.8 | 1.00 |
| 1-2 | 227 | 2026 | 23.3 | 0.78 (0.66-0.92) |
| >2 | 53 | 515 | 21.5 | 0.72 (0.54-0.96) |

Group 4: Blood pressure factors

| Brachial systolic blood pressure, mm Hg | ≤128 | 135 | 1328 | 21.0 | 1.00 |
| >128-140 | 130 | 1281 | 20.9 | 1.00 (0.78-1.27) |
| >140-152 | 124 | 1106 | 23.4 | 1.12 (0.87-1.42) |
| >152-168 | 124 | 850 | 31.0 | 1.48 (1.16-1.89) |
| >169 | 125 | 554 | 50.3 | 2.42 (1.90-3.09) |

| Posterior tibial artery blood pressure, mm Hg | ≤127 | 128 | 576 | 49.5 | 1.00 |
| >127-146 | 127 | 1203 | 21.9 | 0.44 (0.34-0.56) |
| >146-158 | 125 | 1026 | 25.4 | 0.51 (0.40-0.65) |
| >158-168 | 85 | 830 | 21.1 | 0.42 (0.32-0.55) |
| >168 | 124 | 1125 | 23.0 | 0.46 (0.36-0.59) |

| Diuretic use | No | 381 | 3816 | 20.6 | 1.00 |
| Yes | 265 | 1385 | 41.6 | 2.03 (1.74-2.38) |

Group 5: Serum lipid levels

| LDL, mmol/L (mg/dl) | ≤2.48 (96) | 129 | 744 | 36.9 | 1.00 |
| >2.48-3.02 (96-117) | 124 | 983 | 26.3 | 0.71 (0.55-0.91) |
| >3.02-3.46 (117-134) | 125 | 1031 | 25.3 | 0.68 (0.53-0.87) |
| >3.46-3.96 (134-153) | 128 | 1017 | 26.5 | 0.72 (0.56-0.91) |
| >3.96 (153) | 122 | 1326 | 19.0 | 0.51 (0.40-0.66) |

Group 6: diabetes and related serum measures

| Fasting blood glucose, mmol/L (mg/dL) | ≤5.2 (94) | 132 | 1348 | 20.2 | 1.00 |
| >5.2-5.6 (94-100) | 128 | 1147 | 23.2 | 1.15 (0.90-1.46) |
| >5.6-6.0 (100-108) | 124 | 1124 | 22.9 | 1.13 (0.89-1.45) |
| >6.0-7.2 (108-130) | 126 | 937 | 28.4 | 1.41 (1.10-1.79) |
| >7.2 (130) | 126 | 609 | 45.6 | 2.27 (1.78-2.90) |

(Continued)
<table>
<thead>
<tr>
<th>Group 7: other serum measures</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td>Unadjusted RR (95% CI)</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>No. of Deaths</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td><strong>C</strong></td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>156</td>
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<tr>
<td>Creatinine, µmol/L (mg/dL)</td>
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<tr>
<td>Fibrinogen, g/L</td>
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<td>Group 8: disease</td>
<td>597</td>
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<td>ConCPG at risk</td>
<td>49</td>
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<tr>
<td>Coronary heart disease</td>
<td>382</td>
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<tr>
<td>Group 9: noninvasive physiologic measures</td>
<td>568</td>
</tr>
<tr>
<td>Forced vital capacity, mL (spirometry)</td>
<td>78</td>
</tr>
<tr>
<td>Group 10: consequences of disease difficulty with instrumental activities of daily living (self-report), No.</td>
<td>99</td>
</tr>
<tr>
<td><strong>Digit Symbol Substitution test score</strong></td>
<td>210</td>
</tr>
<tr>
<td>Self-assessed health</td>
<td>128</td>
</tr>
</tbody>
</table>

**Table 1.**—Association of Population Characteristics With 5-Year Mortality in 5201 Men and Women Aged 65 Years or Older: Unadjusted and Final Adjusted Models, the Cardiovascular Health Study* (cont)

*RR indicates relative risk; CI, confidence interval; LDL, low-density lipoprotein; ECG, electrocardiographic; and ellipses, data not applicable. Variables in each group entered but not significant in any models were as follows: group 1, race, group 2, height and weight circumferences, bioelectric impedance reactance and resistance, body mass index, and self-reported weight at age 50 years relative to current weight; group 3, smoking—passive, current vs ever; group 4, brachial diastolic blood pressure, history of hypertension, use of any antihypertensive medications, and interaction of diuretic use with systolic blood pressure; group 5, total cholesterol, high-density lipoprotein cholesterol, triglycerides (all in quintiles), and use of lipid-lowering medication; group 6, history of diabetes, fasting insulin; group 7, factor VII, factor V, III, potassium, and uric acid; group 8, asthma, emphysema, angina, myocardial infarction, stroke, transient ischemic attack, claudication, arthritis, renal disease, cancer, hearing impairment, visual impairment, use of any β-blocker, use of any angiotensin-converting enzyme inhibitor; and group 9, forced expiratory volume in 1 second, mitral stenosis and mitral regurgitation (electrocardiography), and maximum stenosis of external carotid artery.

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variable, relative to the reference category. P values given for each variable to test the hypothesis of equal risks across the categories of the variable after adjustment for the other variables in the model. After the completion of the final model, interactions of sex and of coronary heart disease at baseline with other predictors of mortality were assessed and included in the model if P < .01.

To test the proportional hazards assumption of the Cox model, interactions of each variable shown in Table 1 with survival time were computed and allowed to enter the model on a one-at-a-time basis. The statistical significance of these interactions was tested for departures for proportional hazards with the score test. The Bonferroni adjustment of the P value was done for the multiple comparisons involved.

Then, to evaluate the external validity of the model, a risk score was computed by multiplying, for each individual, the regression coefficient from each variable in the Cox model by the value of the corresponding variable for the individual. These products were summed to give a "prognosis score" for each individual. To externally validate the findings from the original CHS cohort, the same approach was taken for each member of the separate CHS African American cohort using the final model given in column F of Table 1 (except left ventricular ejection fraction and aortic stenosis were assumed to be not present, as these variables were not measured at baseline). This cohort was not included in the analyses reported in Table 1. For both cohorts, the risk score was stratified into quintiles, and the mortality in each quintile was computed along with the χ² test for trend.

RESULTS

The 5201 participants were aged 65 to 101 years at baseline, with a mean age of 75 years; 57% were female, 95% were white, and there was a broad distribution of both health and socioeconomic status (Table 1, column C). Twenty-five percent had 1 chronic disease, and 61% had 2 or more chronic diseases. Twenty-three percent reported being in fair or poor health.

After 5 years of follow-up, there were 646 deaths representing 12% of the population. Mortality rates increased with age for both men and women, while survivorship was substantially higher for women in each age group, and 2-fold higher for women overall compared with men (Table 1, column D).

Death rates declined with increasing education and income, with the lowest rates for those with high school education or more, and for those with annual incomes of $50 000 or more (Table 1, column D). Health habits were associated with death rates in stepwise fashion. Specifically, those reporting energy expenditure of more than 7908 kJ/wk (1890 kcal/wk) in moderate or vigorous activities had 5-year death rates of 15.5 per 1000, with stepwise increases in rates for those with lesser amounts. Those with more than 4100 kJ/wk (980 kcal/wk) of energy expended in moderate to vigorous activity had one-half to two-thirds the risk of those with energy expenditures of less than 252 kJ/wk (67.5 kcal/wk). Those who had smoked less than 25 pack-years had half the death rate of those who smoked 50 or more pack-years (<23.0 per 1000 vs 47 per 1000).

Table 1 shows the groups of characteristics that were entered into stepwise Cox models together, with sequential modeling from group 1 to group 2, and so forth. Only variables that were significant in either the unadjusted sequential or final Cox models are listed. Columns E and F show the RRs for mortality for each characteristic significant in any of these models, with column E showing the unadjusted RRs and column F the RRs adjusted for all variables in the final model. Only those variables that were entered and were significant in the final model have numbers displayed in column F. Also displayed are the associated 95% confidence intervals and P values for the test of equality of risks across categories.

Twenty characteristics of 78 initially considered were jointly significant predictors of mortality over 5 years. Those significantly associated included measures from each group of variables hypothesized to be related to mortality except for lipids and ranged from demographic and lifestyle characteristics and risk factors to different aspects of disease: history of clinical disease, direct measurement of clinical and subclinical disease, and consequences of disease.

Several findings were particularly notable. First, age became less strongly associated with mortality after adjustment for other demographic and health characteristics (Figure and Table 1). Second, sex remained significantly associated with mortality after adjustment. Men had a 2.3-fold higher risk of mortality compared with women, and the apparent protective effect of female sex—43% lower risk—persisted, compared with men, after adjustment for disease and other characteristics (Figure and Table 1). There were, however, no significant interactions with any of the other predictors of mortality (data not shown).

In addition, there were strong independent associations of health habits and selected cardiovascular disease risk factors with 5-year mortality in the final models: these included physical activity (a dose-response relationship), more than 50 pack-years of smoking, systolic blood pressure higher than 169 mm Hg, and fasting glucose level greater than 7.2 mmol/L (130 mg/dL). In contrast, LDL cholesterol was not associated with mortality in the final models. However, a negative association of LDL cholesterol with mortality was seen in both the unadjusted (Table 1, column E) and sequential adjusted (data not shown) models. In the latter, LDL cholesterol level higher than 3.96 mmol/L (153 mg/dL) had a significantly lower risk (RR, 0.66), compared with lower values of LDL cholesterol. High-density lipoprotein cholesterol and total cholesterol were not associated with mortality at any point in the modeling.

Only 1 clinical disease, by history, was a significant predictor of mortality in the final models: CHF (RR, 1.67; P < .005; Table 1, column F). There was no interaction of coronary heart disease with other diseases. In contrast, a number of objective, noninvasive measures of severity of cardiovascular and pulmonary disease and of subclinical disease were significant, independent predictors of mortality. These included the presence of a major electrocardiographic abnormality (RR, 1.36), abnormal left ventricular ejection fraction (RR, 1.99) and aortic stenosis (moderate [RR, 3.14] and severe [RR, 7.01]) by echocardiography, maximal stenosis of the internal carotid artery by ultrasound (100% stenosis: RR, 2.39), and forced vital capacity (FVC) (for FVC >3.60 mL vs ≤2.06 mL: RR, 0.60) (see Table 1, group 9, column F).
Table 2.—External Validation of Mortality Prediction in Separate Cardiovascular Health Study (CHS) Cohort of African Americans Compared With Original Cohort

<table>
<thead>
<tr>
<th>Quintile of Risk*</th>
<th>CHS Original Cohort (n=5201)</th>
<th>External Validation Sample: CHS African American Cohort (n=685)</th>
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<tbody>
<tr>
<td></td>
<td>Overall Rate, 5 y of Follow-up, %</td>
<td>Rate per Person-Year, %</td>
</tr>
<tr>
<td>1</td>
<td>17.9</td>
<td>0.4</td>
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<tr>
<td>2</td>
<td>11.8</td>
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<tr>
<td>4</td>
<td>11.9</td>
<td>1.3</td>
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<tr>
<td>5</td>
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<td>...</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
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</tbody>
</table>

*Based on calculation of risk score (see “Methods”).

for 95% confidence intervals). Objective measures of disease that were not associated with mortality were forced expiratory volume in 1 second (with FVC also in the model), mitral stenosis, and mitral regurgitation (by echocardiography). Ankle-arm blood pressure index was not predictive of mortality when brachial and posterior tibial systolic blood pressure were also in the model.

Higher weight was associated with lower risk of mortality, with the heaviest men (>85.5 kg [190 lb]) and women (>75.6 kg [168 lb]) having almost half the mortality risk of those weighing 63.0 or 51.8 kg (142 or 115 lb) or less, respectively.

Two biochemical measures of disease and its consequences, creatinine and albumin, were also predictive of mortality. Creatinine level higher than 133 µmol/L (1.5 mg/dL) was associated with a 71% higher risk of mortality, compared with those with creatinine level less than 80 µmol/L (0.9 mg/dL). It is notable that even a “mildly elevated” creatinine reading between 106 and 133 µmol/L (1.2 and 1.5 mg/dL) was associated with a 35% increase in mortality risk, compared with those with a creatinine level less than 80 µmol/L (0.9 mg/dL). Those with an albumin level higher than 42 g/L had one-half the risk of mortality of those with albumin levels less than 37 g/L.

Both physical and cognitive function were independently associated with 5-year mortality, adjusting for all other characteristics entered into the final models (Table 1, group 10, column F). Specifically, difficulty with 2 or with 3 or more instrumental activities of daily living (tasks essential to home management and independent living) was associated with mortality, with RR of 1.46 and 1.64, respectively (P < .001), compared with those with no or 1 difficulty. In addition, cognitive function, as measured by score on the Digit Symbol Substitution test, was inversely associated with mortality; those with the best function, scores higher than 40, had almost half the risk of mortality of those with scores less than 18 (P < .001). A protective association was seen for those with scores of 26 or greater. Neither the Mini-Mental State Examination score nor walking speed was associated with mortality in the final models in the presence of these other variables.

Of the 26 variables that were significantly associated with mortality in unadjusted models, 6 were no longer significant in the final model in the presence of the other variables. This included LDL cholesterol level and history of coronary heart disease, education, widowhood, alcohol use, and fibrinogen level. However, related variables were still significantly associated in the final model; for example, income remained in the model while education did not, and abnormal ejection fraction and major electrocardiographic abnormalities were significant while the clinical diagnosis of coronary heart disease, broadly, was not longer significant in their presence.

The tests for violation of the proportional hazards assumption did not reach statistical significance. Thus, there was no evidence of any important deviations from the proportional hazards assumption.

Finally, we evaluated the external validity of the final model by applying the risk stratification resulting from this model in the original CHS cohort to a separate African American cohort. The results of risk stratification for both cohorts are shown in Table 2. For the African American cohort, during 4.25 years of follow-up, the death rate ranged from 0% in the lowest-risk quintile to 26.3% for the highest quintile (test for trend: χ² = 56, P < .001). For the original cohort the results were similar, with the death rate (for 5 years of follow-up) ranging from 1.9% in the lowest-risk quintile to 38.9% for the highest-risk quintile (test for trend, χ² = 660, P < .001).

COMMENT

We report here the multiple characteristics jointly predictive of 5-year mortality in community-dwelling adults aged 65 years or older. The risk prediction score derived from the characteristics jointly associated with mortality showed substantially increased mortality risk from lowest to highest quintiles, in both the original and the external validation cohorts.

The strongest predictors of mortality included noninvasive, objective measures of both subclinical and clinical chronic diseases, by echocardiography, electrocardiography, brachial and tibial blood pressures, carotid ultrasound, sphygmometry, fasting glucose level, creatinine level, and cognitive function evaluation. These direct, objective measures of disease generally replaced clinical history as predictors of mortality. This has a number of potential explanations. These measures are not subject to false negatives or false positives to the degree that clinical history might be. They represent current status, rather than mixing what may be events far in the past with more recent ones, as clinical history (yes or no) can do. These measures also objectively quantitate levels of disease severity and the presence of subclinical disease, providing unique information in predicting mortality. Thus, we report here increasing risk of mortality with increasing severity of albumin decline, creatinine elevation, aortic stenosis, maximal stenosis of the internal carotid artery, and lower cognitive function. Other disease measures showed a threshold association with mortality: elevated brachial systolic blood pressure (>169 mm Hg), low posterior tibial artery blood pressure (<127 mm Hg), moderate or severe aortic stenosis, elevated fasting blood glucose level (>7.2 mmol/L [130 mg/dL]), and low FVC (<3.0 mL). These findings identify clinical levels of risk that are associated with higher mortality and, therefore, should be considered in setting treatment goals or monitoring their effects.

That the severity of carotid atherosclerosis (as determined by ultrasound) displaced history of stroke and transient ischemic attack suggests that it may provide a more specific causal link—as an indicator of severity and/or mechanism—with mortality than disease history at baseline, although it has previously been shown that carotid atherosclerosis is associated with prevalent stroke and transient ischemic attack. However, the strongly positive RR for maximum stenosis of the internal carotid artery decreased substantially after ad-
rather, the sex differential persisted un-
tics. This did not occur in this study.
were the major explanations, the risk for
systolic blood pressure and fasting glu-
sclerosis, cardiovascular risk factors (eg,
work suggested that the better survival
of female sex on mortality persisted af-
conducted in male populations.
ment therapy.
consideration is the role of hormone replace-
mortality in older adults. Our findings
disease characteristics that jointly, as
justment for other variables, suggesting
whether physical activity levels re-
ported at the onset of the study were
important in themselves or were indica-
tors of the individual’s lifetime history of
exercise. It is also possible that the as-
so of low physical activity with
mortality could reflect the effects of ill-
nesses present at baseline, rather than
the primary effects of the risk factor. While
we were able to adjust for pres-
ence and severity of a number of dis-
eases, thus minimizing confounding, it is
not possible in these analyses to defini-
tively tease out the independent role of
low physical activity when disease was
jointly present.
Those with current annual incomes of
$50 000 or higher per year had substanc-
tially lower risk of mortality than those
with lower incomes, with income displac-
ing education as a predictor. In separate
analyses, there were no important dif-
fences in risk for subgroups of annual
income less than $50 000. While consist-
tent with prior studies, behavioral and
social risk factors have not been evalu-
ated previously in the presence of so
many other potential risk factors, includ-
ing directly measured disease.
In terms of other classic cardiovascu-
lar disease risk factors, higher levels
(>3.96 mmol/L [153 mg/dL]) of LDL cho-
esterol showed two-thirds the mortal-
ity risk of levels less than 2.48 mmol/L
(96 mg/dL) in the adjusted (not final)
alyses, with no evidence of a nonlinear
relationship. This has been previously
reported for older adults, but is consis-
tent with the observation that ill-
nesses that cause mortality may also
lower the LDL cholesterol level. How-
ever, in the final models LDL cho-
sterol was not a significant predictor of
mortality. Low LDL cholesterol levels
are associated, cross-sectionally, with
lower levels of albumin as well as factor
VII, diabetes, and prevalent cancer.32
Therefore, the lack of association of LDL
cholesterol with mortality in the final
models may be a result of competition in
the models with other variables, as well
as a different import of LDL cholesterol
levels in the older population.
Low weight was also strongly and in-
dependently predictive of mortality,
while height was not. A negative rela-
tionship between weight and survival
time, independent of height or body
mass index, may be consistent with the
occurrence of weight loss as a result of
disease.25 Interestingly, this study does
not show an association of obesity with
mortality, as some other studies do.26,27
Albumin’s relationship with mortality in
this study was inverse and graded, par-
allel to that of weight. This association
held even after adjusting for the sever-
ity of a number of diseases that can cause
low albumin. It has been hypothesized
that albumin may have an independent
etiologic role in mortality, as well as be-
low an indicator of severe disease.28 Both
low weight and low albumin may be in-
dicators of the frailty of the individual
and have previously been shown to be
predictors of mortality.25
That there was no association of can-
cer with 5-year mortality in this study
was likely a result of study selection cri-
teria, in that persons with cancer under
active treatment were excluded from
the study at the time of recruitment.
Diuretic use was associated with a
67% increased risk of mortality over 5
years, adjusting for blood pressure and
CHF history as well as other variables in
the final model. We explored this finding
further, considering separately those
with and without CHF. The RR for di-
uretic use remained significant among
those with no CHF (hazard ratio, 1.38
after adjustment; P < .001). The excess
risk was entirely in those without hyper-
tension or CHF who were taking diuret-
ics (n = 211) (unadjusted RR, 4.35;
P < .001). In contrast, the hazard ratio
for diuretic use among those with hyper-
tension alone was very near to 1. Those
with CHF had a substantially higher risk
for diuretic users, compared with non-
users (hazard ratio, 2.48; P = .02); this
could be consistent with the use of di-
uretics in more severe CHF. Thus, it is
possible that the risk associated with di-
uretic use is a reflection of the severity of
the underlying disease for which it is a
therapy, eg, CHF or liver disease.
The independent association of mor-
tality with a measure of early cognitive
impairment, the Digit Symbol Substitu-
tion test, adjusting for age and educa-
tion, is intriguing. This test assesses vi-
ual-motor speed and coordination, vi-
ual search, and cognitive flexibility.44 It
is the most age-sensitive of the subtests
of the Wechsler Adult Intelligence
Scale–Revised and is considered a mea-
sure of intellectual ability.19 It distin-
guishes mild, Alzheimer-type dementia
from benign cognitive changes of normal
aging.25 Relationships of cognitive im-
pairment with mortality have previ-
ously been reported, but adjusting for
far fewer diseases and other character-
istics44 or using less sensitive measures
of cognitive impairment.26 It is notable
that only the more sensitive Digit Sym-
bol Substitution test and not the Mini-
Mental State Examination was related
to mortality in this study. Similar to find-
ings by Schoenfeld et al,26 we find an as-
sociation of subclinical cognitive deficits
(scores of 26 and higher) with mortality.
Mortality in Older Adults—Fried et al
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logical function, or age-related slowing of cognitive processing as a marker for other age-related processes that, in themselves, independently predict mortality. Alternatively, cognitive impairment may be causal in itself, by impact on such factors as health care compliance and health practices.

Interestingly, the measure of physical functioning that was associated with mortality, difficulty with instrumental activities of daily living, is the one also most associated with cognitive impairment. It is not known whether difficulty with instrumental activities of daily living is a marker for severity of cognitive impairment, whether it represents the severity of other diseases that may cause disability, or whether physical disability is playing an independent etiologic role in mortality. Other studies have shown that disability in instrumental activities of daily living predicts mortality. However, it has not been previously demonstrated that this is an independent effect over and above the contribution of cognition and the severity of objectively measured chronic diseases.

Most older persons die as a consequence of a combination of factors, and the recorded cause of death may be the precipitant at the end of a long series of different illnesses and multiple system failures. For these reasons, the immediate cause of death may be less explanatory in older than in younger persons, and the longer-term predictors may be as important. The finding in this study of a number of characteristics independently and jointly predicting mortality over 5 years is consistent with the frequent clinical picture of multiple contributing causes of death. In fact, at least 1 characteristic from 9 of the 10 groups that were analyzed were independently associated with mortality risk, after adjusting for the other characteristics in the model. The finding that subclinical disease is an independent source of prognostic information regarding mortality risk in older adults provides insight into its potential import and carries the implication that secondary prevention at the stage of subclinical or early clinical disease may have value as a clinical strategy.

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