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 (>169 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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THE HEALTH STATUS of older adults is complex. Older adults frequently have multiple subclinical and clinical diseases and consequent disability. Related to this comorbidity, it is rare for a single aspect of health status to be the sole predictor of adverse outcomes in older adults, including mortality.[1,2] And yet the joint contributions of diseases and disability to mortality have not been well studied. In addition, few population-based studies have this information on mortality risk that could be derived from objectively measured clinical or subclinical diseases, as opposed to clinical history,[1,3-8] especially jointly with other factors. The latter approach would provide insight on both the extent to which multiple factors contribute to mortality in older adults and the prognostic importance of objectively measured, quantitated subclinical disease, such as atherosclerosis or forced vital capacity (FVC).

For editorial comment see p 622.

This article reports on the independent, joint contributions to total mortality over 5 years of subclinical, clinical, and end-stage disease, measures of frailty, impairments of physical and cognitive function, and sociodemographic characteristics, including sex, health habits, and cardiovascular disease risk factors, in a multicenter study of community-dwelling men and women aged 65 to 101 years at baseline.

METHODS

Study Population

The Cardiovascular Health Study (CHS) is a prospective, observational study designed to determine the risk factors for and consequences of cardiovascular disease in older adults. In 1989 and 1990, a total of 5201 men and women aged 65 years or older were recruited in 4 US communities to participate in CHS: Sac-

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ramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Allegheny County (Pittsburgh), Pennsylvania. Potential participants were identified from a random sample stratified by age group (65-74, 75-84, ≥85 years) from the Health Care Financing Administration (HCFA) Medicare Enrollment Lists. All persons thus identified and age-eligible household members who were planning to reside in the community for at least 3 years were eligible to participate. Exclusion criteria included being wheelchair bound in the home, unable to participate in the examination at the field center, or undergoing active treatment for cancer. Fifty-seven percent of eligible subjects agreed to participate.[9]

Participants tended to be healthier and better educated than those who refused, although there was still a substantial amount of chronic disease reported by participants at baseline.[9] Details of the sampling and recruitment have been published previously.[9,10]

A supplemental cohort of 685 African American men and women were recruited in 1992 and 1993 from 3 of the CHS communities (all except Washington County) using the same sampling and recruitment methods. As the length of follow-up on this group is only half as long and because echocardiograms were not performed on this additional group at baseline, this group was not included in the central analyses for this article. Data from the supplemental cohort were evaluated, however, as an external validation sample (see below).

Evaluation

Participants completed standardized interviews by trained interviewers and an extensive examination at the field center. Interviews included demographic characteristics, self-assessed health status, health habits, physical activity, physical function, and medications used, and self-report of physician diagnosis of myocardial infarction, angina, congestive heart failure (CHF), hypertension, stroke, transient ischemic attack (TIA), asthma, emphysema, diabetes, intermittent claudication, renal disease, arthritis, hearing impairment, visual impairment, and cancer.[10]

Self-report of cardiovascular and pulmonary diseases was validated according to standardized criteria by ascertaining medications used and by relevant standardized examinations performed on all participants: electrocardiogram,[11,12] echocardiogram,[13] spirometry,[14] posterior tibial–brachial artery systolic (ankle-arm) blood pressure ratio, and/or medical record review.[11] Protocols for these examinations have been previously published. Diabetes was defined by the presence of fasting glucose level greater than 7.8 mmol/L (140 mg/dL), or a glucose level of 11.1 mmol/L (200 mg/dL) or higher 2 hours after ingestion of a 75-g (approximately 7 oz) glucose load in a flavored drink, or history of diabetes or taking insulin or oral hypoglycemic agents. Medical records were reviewed and standardized criteria applied, when needed, to adjudicate the presence of self-reported cardiovascular diseases.

Additional examination measures obtained included blood pressure using a Hawksley random-zero sphygmomanometer. Carotid ultrasound was performed[15] to measure the maximal stenosis of the internal and common carotid arteries. Phlebotomy was performed under fasting conditions, and the blood was analyzed by the Laboratory for Clinical Biochemistry Research at the University of Vermont for levels of fasting glucose, total cholesterol, high-density lipoprotein cholesterol, serum albumin, creatinine, and fibrinogen.[16] Fasting plasma lipid analyses were performed, and low-density lipoprotein (LDL) cholesterol was calculated.[16] Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale questionnaire.[17] Finally, cognitive function was assessed with the Mini-Mental State Examination[18] and the Digit Symbol Substitution subtest of the Wechsler Adult Intelligence Scale–Revised.[19] Performance-based measures of physical function included a 4.6-m (15-ft) measured walk at usual pace (timed to the 0.1 second) and the average of 3 measures of maximal grip strength in the dominant hand (to the nearest kilogram), using a Jamar dynamometer.[10]

Ascertainment and Verification of Mortality

Participants were reinterviewed every 6 months. Confirmation of deaths 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 presented 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

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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*

A Variable	B No. of Deaths	C No. at Risk	D Death Rate (per 1000 Person-Years)	E Unadjusted RR (95% CI)	E P Value	F Final Model RR (95% CI)	F P Value
Group 1: demographic and social factors							
Age, y							
65-69	123	1835	13.6	1.00		1.00	
70-74	155	1616	19.8	1.46 (1.15-1.85)		1.15 (0.90-1.47)	
75-79	172	1061	34.8	2.59 (2.05-3.26)	<.001	1.46 (1.13-1.87)	<.001
80-84	120	496	54.5	4.08 (3.17-5.25)		1.72 (1.29-2.29)	
≥85	76	193	96.6	7.35 (5.52-9.79)		2.56 (1.82-3.61)	
Sex							
Female	247	2962	17.2	1.00	<.001	1.00	<.001
Male	399	2239	38.2	2.24 (1.91-2.63)		2.34 (1.84-2.98)	
Education							
<High school	250	1438	37.3	1.00		. . .	. . .
High school or college	341	3224	22.0	0.59 (0.50-0.69)	<.001	. . .	. . .
Postgraduate	55	525	21.6	0.58 (0.43-0.77)		. . .	. . .
Annual income, $							
<50 000	549	4174	27.6	1.00	<.001	1.00	<.05
≥50 000	51	682	15.2	0.55 (0.41-0.73)		0.73 (0.54-0.98)	
Widowhood							
No	463	4004	24.0	1.00	<.001	. . .	. . .
Yes	183	1197	32.8	1.37 (1.15-1.63)		. . .	. . .
Group 2: anthropometric variables							
Weight, kg (lb)							
Men / Women							
≤63.9 (142) / ≤51.8 (115)	127	596	46.6	1.00		1.00	
>63.9-70.2 (142-156) / >51.8-49.0 (115-131)	129	943	28.8	0.61 (0.48-0.78)		0.87 (0.67-1.12)	
>70.2-77.4 (156-172) / >59.0-65.2 (131-145)	128	1130	23.6	0.50 (0.39-0.64)	<.001	0.63 (0.48-0.81)	<.001
>77.4-85.5 (172-190) / >65.2-75.6 (145-168)	134	1354	20.5	0.43 (0.34-0.55)		0.59 (0.45-0.77)	
>85.5 (190) / >75.6 (168)	126	1163	22.5	0.48 (0.37-0.61)		0.56 (0.43-0.75)	
Group 3: Lifestyle factors							
Physical activity, kJ (kcal)/wk in moderate or vigorous exercise							
≤282 (67.5)	130	566	52.1	1.00		1.00	
>282-1789 (67.5-472.5)	130	846	32.8	0.62 (0.49-0.80)		0.78 (0.60-1.00)	
>1789-4100 (472.5-980.0)	127	936	28.7	0.55 (0.43-0.70)	<.001	0.81 (0.63-1.05)	<.005
>4100-7908 (980.0-1890.0)	129	1168	22.9	0.43 (0.34-0.55)		0.72 (0.55-0.93)	
7908 (1890.0)	128	1669	15.5	0.29 (0.23-0.38)		0.56 (0.43-0.74)	
Pack-years smoking							
Never smoked	246	2358	21.7	1.00		1.00	
1-25	124	1119	23.0	1.06 (0.85-1.32)	<.001	1.10 (0.88-1.38)	<.005
26-50	127	952	28.0	1.29 (1.04-1.60)		1.13 (0.90-1.43)	
>50	138	645	46.6	2.07 (1.65-2.58)		1.58 (1.25-2.00)	
Alcohol, drinks/d							
None	351	2489	29.8	1.00		. . .	. . .
≤1	227	2026	23.3	0.78 (0.66-0.92)	<.005	. . .	. . .
>1-3	53	515	21.5	0.72 (0.54-0.96)		. . .	. . .
>3	12	153	15.9	0.53 (0.30-0.94)		. . .	. . .
Group 4: Blood pressure factors							
Brachial systolic blood pressure, mm Hg							
≤128	135	1328	21.0	1.00		1.00	
>128-140	130	1281	20.9	1.00 (0.78-1.27)		0.88 (0.68-1.13)	
>140-152	124	1106	23.4	1.12 (0.87-1.42)	<.001	0.98 (0.75-1.27)	<.001
>152-168	124	850	31.0	1.48 (1.16-1.89)		1.15 (0.87-1.51)	
>169	125	554	50.3	2.42 (1.90-3.09)		1.56 (1.17-2.08)	
Posterior tibial artery blood pressure, mm Hg							
≤127	128	576	49.5	1.00		1.00	
>127-146	127	1203	21.9	0.44 (0.34-0.56)		0.79 (0.61-1.03)	
>146-158	125	1026	25.4	0.51 (0.40-0.65)	<.001	0.99 (0.76-1.29)	<.05
>158-168	85	830	21.1	0.42 (0.32-0.55)		0.83 (0.62-1.11)	
>168	124	1125	23.0	0.46 (0.36-0.59)		0.68 (0.51-0.90)	
Diuretic use							
No	381	3816	20.6	1.00	<.01	1.00	<.001
Yes	265	1385	41.6	2.03 (1.74-2.38)		1.67 (1.29-2.16)	
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)	<.001	. . .	. . .
>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		1.00	
>5.2-5.6 (94-100)	128	1147	23.2	1.15 (0.90-1.46)		1.10 (0.85-1.41)	
>5.6-6.0 (100-108)	124	1124	22.9	1.13 (0.89-1.45)	<.001	1.05 (0.81-1.35)	<.001
>6.0-7.2 (108-130)	126	937	28.4	1.41 (1.10-1.79)		1.26 (0.97-1.64)	
>7.2 (130)	126	609	45.6	2.27 (1.78-2.90)		1.86 (1.43-2.43)	

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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)

A Variable	B No. of Deaths	C No. at Risk	D Death Rate (per 1000 Person-Years)	E Unadjusted RR (95% CI)	E P Value	F Final Model RR (95% CI)	F P Value
Group 7: other serum measures							
Albumin, g/L							
≤37	156	939	35.1	1.00		1.00	
>37-39	149	1229	25.2	0.71 (0.57-0.89)		0.71 (0.56-0.89)	
>39-40	95	727	27.5	0.78 (0.60-1.00)	<.001	0.83 (0.64-1.08)	<.001
>40-42	139	1261	23.1	0.65 (0.52-0.82)		0.63 (0.50-0.80)	
>42	97	1009	20.1	0.57 (0.44-0.73)		0.54 (0.42-0.71)	
Creatinine, μmol/L (mg/dL)							
≤80 (0.9)	157	2135	15.1	1.00		1.00	
>80-97 (0.9-1.1)	171	1417	25.2	1.68 (1.35-2.08)		1.31 (1.04-1.66)	
>97-106 (1.1-1.2)	59	510	24.0	1.60 (1.18-2.15)	<.001	1.01 (0.73-1.39)	<.005
>106-133 (1.2-1.5)	143	801	38.0	2.55 (2.03-3.19)		1.35 (1.04-1.75)	
>133 (1.5)	106	302	85.0	5.77 (4.51-7.38)		1.71 (1.28-2.30)	
Fibrinogen, g/L							
≤2.9	141	1644	17.6	1.00		. . .	. . .
>2.9-3.1	114	1068	22.4	1.28 (1.00-1.63)		. . .	. . .
>3.1-3.5	129	1010	26.5	1.52 (1.20-1.93)	<.001	. . .	. . .
>3.5-4.0	138	874	33.3	1.91 (1.51-2.42)		. . .	. . .
>4.0	109	544	44.4	2.56 (1.99-3.29)		. . .	. . .
Group 8: disease							
Congestive heart failure							
No	597	5097	24.4	1.00	<.001	1.00	<.005
Yes	49	104	129.2	5.50 (4.11-7.36)		1.67 (1.29-2.16)	
Coronary heart disease							
No	382	3871	20.4	1.00	<.001	. . .	. . .
Yes	264	1330	43.5	2.16 (1.84-2.52)		. . .	. . .
Group 9: noninvasive physiologic measures							
Forced vital capacity, mL (spirometry)							
≤2.06	124	708	38.0	1.00		1.00	
>2.06-2.54	124	1040	25.0	0.65 (0.51-0.84)		0.82 (0.63-1.06)	
>2.54-3.00	124	1119	23.1	0.60 (0.47-0.78)	<.001	0.78 (0.59-1.04)	<.005
>3.00-3.60	124	1070	24.2	0.63 (0.49-0.81)		0.55 (0.41-0.75)	
>3.60	124	1157	22.0	0.57 (0.45-0.74)		0.60 (0.43-0.83)	
Ejection fraction abnormal (echocardiogram)							
No	568	5011	23.6	1.00	<.001	1.00	<.001
Yes	78	190	106.1	4.64 (3.66-5.88)		1.99 (1.51-2.60)	
Aortic stenosis (echocardiogram)							
None	613	5084	25.2	1.00		1.00	
Mild	15	66	51.6	2.07 (1.24-3.46)	<.001	1.16 (0.68-2.00)	<.001
Moderate	8	19	106.1	4.33 (2.15-8.69)		3.14 (1.49-6.62)	
Severe	5	7	238.5	10.08 (4.18-24.30)		7.01 (2.68-18.36)	
Major ECG abnormality							
No	329	3723	18.1	1.00	<.001	1.00	<.001
Yes	317	1478	47.5	2.65 (2.27-3.09)		1.36 (1.15-1.62)	
Maximum stenosis of the internal carotid artery (ultrasound), %							
0	99	1656	12.2	1.00		1.00	
1-24	210	1790	24.4	2.01 (1.59-2.56)		1.37 (1.07-1.75)	
25-49	228	1350	36.3	3.00 (2.37-3.80)	<.001	1.47 (1.15-1.89)	<.001
50-74	58	235	55.0	4.59 (3.32-6.35)		1.83 (1.29-2.60)	
75-99	14	58	53.8	4.48 (2.56-7.83)		1.71 (0.95-3.08)	
100	12	25	125.7	10.71 (5.88-19.50)		2.39 (1.26-4.53)	
Group 10: consequences of disease							
Difficulty with instrumental activities of daily living (self-report), No.							
≤1	367	3865	19.6	1.00		1.00	
2	181	1000	39.2	2.02 (1.69-2.41)	<.001	1.46 (1.20-1.78)	<.001
≥3	97	327	69.2	3.60 (2.88-4.51)		1.64 (1.26-2.14)	
Digit Symbol Substitution test score							
≤18	127	381	77.8	1.00		1.00	
>18-26	121	618	42.3	0.54 (0.42-0.69)		0.86 (0.66-1.11)	
>26-33	112	859	27.3	0.35 (0.27-0.45)	<.001	0.74 (0.56-0.97)	<.005
>33-40	122	1121	22.6	0.29 (0.22-0.37)		0.72 (0.55-0.95)	
>40	113	1991	11.5	0.14 (0.11-0.19)		0.55 (0.41-0.74)	
Self-assessed health							
Excellent	48	740	13.1	1.00		1.00	
Very good	109	298	17.3	1.32 (0.94-1.85)		1.11 (0.79-1.57)	
Good	216	1941	23.1	1.77 (1.29-2.42)	<.001	1.11 (0.80-1.53)	<.001
Fair	202	1035	42.4	3.27 (2.39-4.48)		1.27 (0.91-1.78)	
Poor	68	177	95.8	7.52 (5.20-10.88)		1.91 (1.27-2.87)	

*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, hip and waist circumferences, bioelectric impedance resistance and reactance, 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 VIII, 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 (echocardiography), 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 χ^2 test for trend.

RESULTS

The 5201 participants were aged 65 to 101 years at baseline, with a mean age of 73 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).

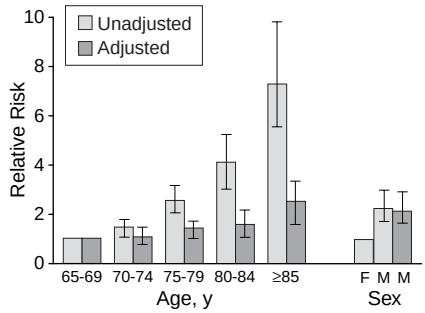
Death rates declined with increasing education and income, with the lowest rates for those with high school education or more, and for those with annual incomes of $50 000 or more (Table 1, column D). Health habits were associated with death rates in stepwise fashion. Specifically, those reporting energy 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 282 kJ/wk (67.5 kcal/wk). Those who had smoked less than 26 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 of sex 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.



Association of age and sex with 5-year mortality in older adults, both with and without adjustment for other variables (see Table 1, columns E and F for data). Age is evaluated in 5-year categories. Male sex remained associated with substantial mortality risk, compared with females, while age became less strongly associated with mortality, after adjustment for other demographic, disease, function, and behavioral characteristics. In these analyses, females are the reference group, and relative risk is expressed for males (compared with females) in unadjusted and adjusted analyses. Error bars indicate 95% confidence limits. The height of the bars indicates the relative risk for each category.

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, maximum 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

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Table 2.—External Validation of Mortality Prediction in Separate Cardiovascular Health Study (CHS) Cohort of African Americans Compared With Original Cohort

	Mortality Rate			
	CHS Original Cohort (n=5201)		External Validation Sample: CHS African American Cohort (n=685)	
Quintile of Risk*	Overall Rate, 5 y of Follow-up, %	Rate per Person-Year, %	Overall Rate, 4.25 y of Follow-up, %	Rate per Person-Year, %
1	1.9	0.4	0	0
2	2.9	0.6	5.8	1.4
3	6.4	1.3	8.0	1.9
4	11.9	2.5	18.2	4.7
5	38.9	9.5	26.3	7.1
χ^2 for trend	659.73	. . .	55.97	. . .
P	<.001	. . .	<.001	. . .

*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 RRs 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 no 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: $\chi^2=56$, $P<.001$). 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, $\chi^2=660$, $P<.001$).

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, spirometry, 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.[20] However, the strongly positive RR for maximum stenosis of the internal carotid artery decreased substantially after ad-

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justment for other variables, suggesting further that this measure is a marker for serious atherosclerosis throughout the vasculature, rather than being directly the cause of death.

To our knowledge, this study is the first to provide insight into the multiple disease characteristics that jointly, as well as independently, contribute to mortality in older adults. Our findings are consistent with prior observations that death frequently results from multiple causes at the oldest ages.[2] The findings in this study regarding the associations of individual, directly measured diseases with mortality are also consistent with prior reports,[3-6,21] primarily conducted in male populations.

It is notable that the protective effect of female sex on mortality persisted after adjustment for disease status. Prior work suggested that the better survival of women than men is attributable, in large part, to sex differentials in atherosclerosis, cardiovascular risk factors (eg, systolic blood pressure and fasting glucose level), and sex hormones, and to men being in poorer health.[22-24] If these were the major explanations, the risk for men should move toward 1.0 after adjustment for many of these characteristics. This did not occur in this study. Rather, the sex differential persisted undiminished when adjusting for a number of objectively measured diseases, including characteristics assessed by others,[23,24] suggesting that severity of atherosclerosis and cardiovascular risk factors are not major factors in explaining the sex differential in mortality. In addition, there were no significant interactions of sex with any of the disease variables analyzed, providing evidence that the factors studied did not have a different impact on women than men. Overall, these findings suggest that there must be other unmeasured factors that contribute to the greater longevity of women. One exogenous factor for future consideration is the role of hormone replacement therapy.

In contrast, the association of age with mortality became substantially weaker with adjustment than when analyzed in isolation. Thus, much of the effect of age on mortality is explained by the other disease and personal characteristics jointly considered in this analysis. This suggests that, if it were not for the diseases and health habits that were assessed, people might live considerably longer.

It is noteworthy that certain health habits remained predictive of mortality even into the oldest ages. Both regular exercise and smoking were independently associated with risk of mortality, consistent with prior reports.[25,26] What cannot be differentiated in this study is whether physical activity levels reported at the onset of the study were important in themselves or were indicators of the individual's lifetime history of exercise. It is also possible that the association of low physical activity with mortality could reflect the effects of illnesses present at baseline, rather than the primary effects of the risk factor. While we were able to adjust for presence and severity of a number of diseases, thus minimizing confounding, it is not possible in these analyses to definitively 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 substantially lower risk of mortality than those with lower incomes, with income displacing education as a predictor. In separate analyses, there were no important differences in risk for subgroups of annual income less than $50 000. While consistent with prior studies, behavioral and social risk factors have not been evaluated previously in the presence of so many other potential risk factors, including directly measured disease.

In terms of other classic cardiovascular disease risk factors, higher levels (>3.96 mmol/L [153 mg/dL]) of LDL cholesterol showed two-thirds the mortality risk of levels less than 2.48 mmol/L (96 mg/dL) in the adjusted (not final) analyses, with no evidence of a nonlinear relationship. This has been previously reported for older adults[21,27,28] and is consistent with the observation that illnesses that cause mortality may also lower the LDL cholesterol level.[28] However, in the final models LDL cholesterol 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.[28] 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 independently predictive of mortality, while height was not. A negative relationship 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.[29] Interestingly, this study does not show an association of obesity with mortality, as some other studies do.[30-32]

Albumin's relationship to mortality in this study was inverse and graded, parallel to that of weight. This association held even after adjusting for the severity 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 being an indicator of severe disease.[33] Both low weight and low albumin may be indicators of the frailty of the individual and have previously been shown to be predictors of mortality.[33]

That there was no association of cancer with 5-year mortality in this study was likely a result of study selection criteria, 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 diuretic use remained significant among those with no CHF (hazard ratio, 1.38 after adjustment; $P<.001$). The excess risk was entirely in those without hypertension or CHF who were taking diuretics (n=211) (unadjusted RR, 4.35; $P<.001$). In contrast, the hazard ratio for diuretic use among those with hypertension alone was very near to 1. Those with CHF had a substantially higher risk for diuretic users, compared with nonusers (hazard ratio, 2.48; $P=.02$); this could be consistent with the use of diuretics in more severe CHF. Thus, it is possible that the risk associated with diuretic 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 mortality with a measure of early cognitive impairment, the Digit Symbol Substitution test, adjusting for age and education, is intriguing. This test assesses visual-motor speed and coordination, visual search, and cognitive flexibility.[34] It is the most age sensitive of the subtests of the Wechsler Adult Intelligence Scale–Revised and is considered a measure of intellectual ability.[19] It distinguishes mild, Alzheimer-type dementia from benign cognitive changes of normal aging.[35] Relationships of cognitive impairment with mortality have previously been reported, but adjusting for far fewer diseases and other characteristics[34] or using less sensitive measures of cognitive impairment.[36] It is notable that only the more sensitive Digit Symbol Substitution test and not the Mini-Mental State Examination was related to mortality in this study. Similar to findings by Schoenfeld et al,[36] we find an association of subclinical cognitive deficits (scores of 26 and higher) with mortality. This association may represent primary brain disease or, alternatively, systemic disease with secondary decrease in neu-

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rologic function, or age-related slowing of cognitive processing as a marker for other age-related processes that, in themselves, are predictive of mortality. Alternatively, cognitive impairment may be causal in itself, by impact on such factors as health care compliance and health practices.[35]

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.[37] 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 such 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.[38] 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,[1,2] 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 was 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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