Published in final edited form as:

J Am Geriatr Soc. 2013 May ; 61(5): 739–746. doi:10.1111/jgs.12214.

Nondisease-Specific Problems and All-Cause Mortality in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

C. Barrett Bowling, MD, MSPH^{1,2}, John N. Booth III, MS³, Monika Safford, MD⁴, Heather E. Whitson, MD, MHS^{5,6}, Christine Ritchie, MD, MSPH⁷, Virginia G. Wadley, PhD², Mary Cushman, MD⁸, Virginia Howard, PhD³, Richard M. Allman, MD^{1,2}, and Paul Muntner, PhD³

¹Birmingham/Atlanta Geriatric Research, Education, and Clinical Center, Department of Veterans Affairs Medical Center, Birmingham, AL

²Division of Gerontology, Geriatrics and Palliative Care, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

³Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL

⁴Division of Preventive Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

⁵Division of Geriatrics, Duke University Medical Center, Durham, NC

⁶Geriatric Research Education and Clinical Center, Durham VA Medical Center, Durham, NC

⁷Division of Geriatrics, University of California, San Francisco, San Francisco, CA

⁸Department of Medicine, University of Vermont

Abstract

Background/Objectives—Problems that cross multiple domains of health are frequently assessed in older adults. We evaluated the association between six of these nondisease-specific problems and mortality among middle-aged and older adults.

Design—Prospective, observational cohort

Setting—U.S. population sample

Participants—Participants included 23,669 black and white US adults ≥45 years of age enrolled in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

Measurements—Nondisease-specific problems included cognitive impairment, depressive symptoms, falls, polypharmacy, impaired mobility and exhaustion. Age-stratified (<65, 65–74, and ≥75 years) hazard ratios for all-cause mortality were calculated for each problem individually and by number of problems.

Corresponding author: C. Barrett Bowling, MD, VAMC GRECC/11G, 700 19th Street S, Birmingham, Alabama, 35233, Telephone: (205) 934-3259, Fax: (205) 558-7068, bbowling@uab.edu.

Author Contributions: C. Barrett Bowling, John N. Booth III, Paul Muntner (study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript), Monika Safford, Virginia G. Wadley, Mary Cushman, Virginia Howard, (study concept and design, acquisition of data, analysis and interpretation of data, and preparation of manuscript), Heather E. Whitson, Christine Ritchie, Richard M. Allman (study concept and design, interpretation of data, and preparation of manuscript).

Sponsor's Role: None

Results—Among participants < 65, 65–74, 75 years old, one or more nondisease-specific problems occurred in 40%, 45% and 55% of participants, respectively. Compared to those with none of these problems the multivariable adjusted hazard ratios and 95% confidence intervals for all-cause mortality associated with each additional nondisease-specific problem was 1.34 (1.23–1.46), 1.24 (1.15–1.35) and 1.30 (1.21–1.39), among participants < 65, 65 – 74 years, 75 years of age, respectively.

Conclusion—Nondisease-specific problems were associated with mortality across a wide age spectrum. Future studies should determine if treating these problems will improve survival and identify innovative healthcare models to address multiple nondisease-specific problems simultaneously.

Keywords

nondisease-specific problems; geriatrics; mortality

INTRODUCTION

A geriatric approach to patient care includes evaluation for several problems that cross multiple domains of health, do not fit into discrete disease categories and are often not addressed in routine medical care.^{1–3} Because these problems involve multiple organ systems and are not necessarily the result of a single underlying disease, they have been previously described as “nondisease-specific” health conditions or problems.⁴ Unlike disease-specific diagnoses, nondisease-specific problems include symptoms and impairments that may not meet diagnostic thresholds or are problems that result from the overtreatment of multiple individual diseases. For these problems, the terminology “nondisease-specific” may be more informative than “geriatric” which may imply that they are consequences of the aging process alone.

Examples of nondisease-specific problems that are components of geriatric assessment include cognitive impairment, depressive symptoms, exhaustion, falls and impaired mobility.¹ Polypharmacy is an example of a nondisease-specific problem that results from the treatment of individual diseases among those with multiple conditions.⁴ Prior studies may distinguish between symptoms, impairments and treatment-related problems. However this is a reflection of the disease-oriented model and conceptually, distinctions between these may not be important to patients because each of these problems can cause distress and impact function and quality of life.⁴

Among older adults, these problems, individually, have been shown to be associated with poor health outcomes and the presence of multiple nondisease-specific problems has been shown to be associated with prevalent functional impairment.^{5–10} However there are few data on their co-occurrence and health outcomes. Additionally, these problems have been studied primarily among older populations and there are limited data on the prevalence and mortality risk associated with these problems in middle-aged adults.⁵ Therefore, the goal of the current study was to determine, among middle-aged and older adults, the association of nondisease-specific problems, both individually and in aggregate, with all-cause mortality. To do so, we analyzed data from a large U.S. population sample enrolled in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

METHODS

Study Participants

The REGARDS study was designed to evaluate causes for excess stroke mortality among blacks compared to whites and in the Southeastern U.S. ("Stroke Belt") compared to the remaining continental United States.¹¹ The study enrolled black and white adults 45 years of age and oversampled blacks. Fifty six percent of the sample was recruited from the eight Southern US states, commonly considered as the "Stroke Belt" including the region known as the "Stroke Buckle" (coastal North Carolina, South Carolina, and Georgia) and the remainder of North Carolina, South Carolina, and Georgia along with Alabama, Mississippi, Tennessee, Arkansas and Louisiana. Forty-four percent of the sample was recruited from the other 40 contiguous U.S. states and Washington DC. Participants were randomly selected from a well characterized commercially available list and were drawn as a simple random sample within the three regions (stroke belt, stroke buckle and rest of the nation), so within each of these regions the geographic distribution of the participants is reflective of the general population. Potential participants were mailed an introduction to the study and telephoned within two weeks. Overall cooperation rates (49%) and response rates (33%) were comparable to rates achieved in similar epidemiologic studies.^{11, 12} There were no differences by region in cooperation and participation rates at the telephone enrollment stage of REGARDS.

Between January 2003 and October 2007, 30,239 black (42%) and white (58%) US adults 45 years old were enrolled. We excluded 6,570 participants who did not have available data on all of the nondisease-specific problems, leaving 23,669 for the current analysis. Lack of available data on cognition accounted for most of the missing data (87%) due to its introduction into the REGARDS protocol 11 months subsequent to the initiation of enrollment. The REGARDS study protocol was approved by the Institutional Review Boards at the participating institutions and all participants provided informed consent.

Data Collection

The REGARDS study baseline data were obtained through interview- and self-administered questionnaires and an in-home study visit. Of relevance to the current analysis, age, sex, race, education, household income, and current cigarette smoking were obtained by self-report. Participants were also asked about history of physician-diagnosed hypertension, atrial fibrillation, coronary heart disease, stroke, and diabetes mellitus. During an in-home visit, physical measurements and collection of a fasting blood sample were obtained. Following a standardized protocol, systolic (SBP) and diastolic blood pressure (DBP) were measured twice with the participant in the seated position. The average of the two measurements was calculated and used for analysis. Waist circumference was measured mid-way between the lowest rib and the iliac crest in the standing position. Laboratory measures included serum creatinine, glucose, total and HDL cholesterol, C-reactive protein and urinary albumin and creatinine. Diabetes was defined as taking insulin or oral hypoglycemic agents, or based on the baseline blood collection, a fasting blood glucose ≥ 126 mg/dL or a non-fasting blood glucose ≥ 200 mg/dL. C-reactive protein was measured using a high-sensitivity, particle-enhanced immunonephelometric assay. Atrial fibrillation was defined as self-reported history or evidence on an electrocardiogram (ECG) performed during the in-home assessment.

Six Nondisease-specific problems

The six nondisease-specific problems included cognitive impairment, depressive symptoms, symptoms of exhaustion, history of falls, impaired mobility, and polypharmacy. Cognition was assessed by telephone using the Six-item Screener which evaluates global cognitive

function.¹³ Scores on this scale can range from 0 to 6 with lower scores indicating worse cognition and cognitive impairment defined as a score of 4 or less. The presence of depressive symptoms was defined as a score of 4 or more on the 4-item Center for Epidemiologic Studies Depression Scale (CES-D).¹⁴ Exhaustion was defined as answering “little of the time” or “none of the time” to the Short Form-12 (SF-12) question “How much of the time during the past 4 weeks did you have a lot of energy?”¹⁵ Falls were based on an answer of “yes” to the question “Have you experienced a fall within the past year?” and 2 or more to the question “How many times have you fallen in the last year?” Participants were considered to have impaired mobility if they answered “a lot” among the options of “limited a lot,” “limited a little,” or “not limited at all,” to the SF-12 question “Does your health now limit you in climbing several flights of stairs?” Also, during the in-home visit, participants were asked to provide the bottles for all medications they had taken in the past two weeks, and medication names were recorded and subsequently coded into drug classes. Polypharmacy was defined as the concurrent use of 10 prescription medications.⁷

Outcome Assessment – All-cause mortality

Mortality subsequent to the REGARDS in-home examination was assessed through bi-annual telephone follow-up and contact with proxies provided by the participant upon recruitment. The date of death was confirmed through the social security death index, death certificates, or the national death index. Follow-up for the current analysis was available through March 31, 2011.

Statistical Analyses

Because the six nondisease-specific problems under study are most commonly included as part of a geriatric assessment and to determine if there are differences across age groups, all analyses were conducted stratified by age. Age was divided into three strata (< 65, 65 to 74 and 75 years of age). Within each age stratum, the mean levels or prevalence, as appropriate, of baseline participant characteristics were calculated. Next, the prevalence of each of the six nondisease-specific problems was calculated. Then using age-stratified Cox proportional hazards models, hazard ratios for all-cause mortality were calculated for each condition, separately. Initial models included adjustment for age, sex, race and region of residence with subsequent models including additional adjustment for household income, current cigarette smoking, atrial fibrillation, coronary heart disease, stroke, diabetes, estimated glomerular filtration rate < 60 ml/min.173 m², urinary albumin-to-creatinine ratio 30 mg/g, systolic and diastolic blood pressure, waist circumference, HDL-cholesterol, total cholesterol, and high-sensitivity C-reactive protein (hsCRP).

The percentage of participants with 0, 1, 2, 3 or 4-6 problems was then calculated, separately for each age strata. Participants with 4, 5, or 6 problems were grouped because of the low prevalence of 4 or more nondisease-specific problems after stratifying by age. Age-stratified cumulative incidence curves using the Kaplan-Meier approach, were calculated by number of nondisease-specific problems. Cox proportional hazards models were used to calculate the age-stratified hazard ratios for mortality associated with 1, 2, 3, or 4-6 nondisease-specific problems with 0 problems serving as the referent category. In order to evaluate the impact of adjustment for chronic conditions and physical and biologic measures, models included two levels of adjustment as described above. Proportional hazards assumptions were tested by modeling disease-specific problems by time (log transformed) interaction terms in our multivariable models. The assumption of proportional hazards was violated in two of the more than 20 models conducted in the current analysis. In these cases, both the overall hazard ratio and hazard ratios during 2 years windows of follow-up are presented. Multiplicative interaction between age and nondisease-specific problems was assessed by comparing the log likelihoods for models with and without interaction terms for age by

nondisease-specific problems. Finally, to determine if associations were consistent for whites and blacks and men and women, analyses were conducted further stratified by race and sex. Multiplicative interaction between sex and nondisease-specific problems and race and nondisease-specific problems was assessed by comparing the log likelihoods for models with and without interaction terms for sex by nondisease-specific problems and race by nondisease-specific problems. As a sensitivity analysis, Cox proportional hazards models were repeated excluding participants who died within the first six months of follow up. SAS, version 9.2 (SAS Institute, Cary NC) was used for all analyses.

RESULTS

Participant Characteristics

Of the 23,669 REGARDS study participants included in this analysis, 52%, 31% and 17% of participants were < 65, 65-74 and ≥ 75 years old, respectively (Table 1). Younger participants were more likely to be women and black. Additionally, younger participants were more likely to be current smokers and they had fewer co-morbidities. Younger participants had lower mean systolic blood pressure and higher waist circumference, total cholesterol and hsCRP.

Individual Nondisease-specific problems and All-cause Mortality

The age-specific prevalence of each of the six nondisease-specific problems is displayed in the bottom of Table 1. The prevalence of cognitive impairment, falls, polypharmacy, impaired mobility, and exhaustion was highest among participants ≥ 75 years old. In contrast, the prevalence of depressive symptoms was highest among participants < 65 years old. After adjustment for age, race, sex and geographic region of residence, each of the six problems was associated with an increased hazard ratio for all-cause mortality within each age group (Table 2). After further multivariable adjustment, cognitive impairment, impaired mobility, and exhaustion remained significantly associated with all-cause mortality, regardless of age group. Falls were associated with all-cause mortality among those 65-74 and ≥ 75 years old and depressive symptoms was associated with mortality among those <65 years old.

Co-occurrence of Nondisease-specific problems and All-cause Mortality

Participants in the older age groups had more nondisease-specific problems (Figure 1). Compared to participants with no problems, there was a graded increase in all-cause mortality with increasing number of nondisease-specific problems within each age group (each p-trend <0.001; Figure 2). These associations remained present after multivariable adjustment and there were no significant differences in all-cause mortality across age group (each p for interaction > 0.05) (Table 3 and Supplemental table 1). Similar associations between number of nondisease-specific problems and all-cause mortality were present after excluding those who died in the first six months of follow up (Supplemental table 2).

Subgroup analysis

Among both men and women and whites and blacks, within each age group, a graded increase in mortality was present with more nondisease-specific problems after multivariable adjustment (Supplemental table 3). Interactions between sex and number of nondisease-specific problems and race and nondisease-specific problems on all-cause mortality were not statistically significant (each p for interaction >0.05).

DISCUSSION

In the current study of U.S. adults 45 years of age, six nondisease-specific problems including cognitive impairment, depressive symptoms, exhaustion, falls, impaired mobility and polypharmacy were common and associated with an increased risk for all-cause mortality. Further, there was a higher risk for death with an increasing number of these problems. The presence of multiple nondisease-specific problems was more strongly associated with mortality than any nondisease-specific problem alone. While these problems are most often considered part of a geriatric assessment, we found that they were common among both older and middle-aged participants.

These nondisease-specific problems cross broad domains of health including physical and cognitive impairments, symptoms and treatment-related issues. Thus it is unlikely that a single unifying mechanism can be identified to explain their associations with mortality.⁴ For example, the association between falls and mortality may be related to frailty or related to risk for injury. Depressive symptoms may result in adverse health behaviors or they may be associated with cardiovascular disease risk.¹⁶ Participants taking 10 or more medications are at risk for drug-drug interactions that may increase the risk of death, but polypharmacy is also likely a reflection of both disease severity and the presence of multiple co-occurring conditions, and the association with mortality may reflect this.⁷

Several prior studies have evaluated the associations of individual nondisease-specific problems with mortality and other adverse health outcomes. Cognitive impairment was shown to be associated with mortality among persons 60 years and older.¹⁷ Depressive symptoms have been shown to be associated with mortality and cardiovascular disease events across a broad age range.¹⁸⁻²⁰ Among older adults, falls are associated with functional decline, nursing home placement and death.⁹ Similarly, polypharmacy was shown to be associated with mortality in older populations.⁷ While cross-sectional associations between geriatric conditions, both individually and in aggregate, have been shown to be associated with functional impairment among older adults who were primarily white,⁵ the current study extends these findings to a broad age range using a prospective U.S. population-based sample. Although the hazard ratios were smaller at older age groups, and one may infer that nondisease-specific problems have decreased importance among older adults, a smaller increase in a group with higher baseline mortality may in fact have a greater public health impact.²¹

Further, we have shown a higher risk for death with increasing number of nondisease-specific problems from 0 to 4. There is increasing evidence of the prevalence and importance of multiple co-existing chronic problems among older adults; however prior studies of multimorbidity often only consider disease-specific problems (e.g., diabetes mellitus, osteoarthritis, osteoporosis) or biomarkers.^{22, 23} Because the nondisease-specific problems evaluated in the current study may have shared risk factors, and contribute to cumulative illness burden, persons are likely to be at risk for more than one of these, and it seems clinically relevant to consider these problems together.²⁴ While prior studies evaluated cognitive impairment, depression and walking impairment, as part of an illness burden score,²⁵⁻²⁸ our study included nondisease-specific problems that have been less well studied including polypharmacy and symptoms of exhaustion.

There is growing evidence that individuals with multiple chronic conditions may identify more with problems or outcomes that are not disease-specific.^{29, 30} For example, older adults with diabetes report health concerns and goals related to global function and daily activities rather than disease-specific measures (e.g., hemoglobin A1c level).³¹ Additionally, older adults with multiple chronic problems may view treatment-related problems such as

drug-drug interactions and adverse drug reactions that commonly occur in the setting of polypharmacy as important as disease-specific outcomes.²⁹ Some physicians may consider these problems as less central to health care than traditional disease-specific conditions; however our study provides evidence for an association between these nondisease-specific problems and mortality that was stronger than many of the traditional mortality risk factors included in the analysis.

The current approach to medical care that focuses on the diagnosis and treatment of individual diseases is poorly suited to address these problems. Innovative healthcare models that involve interdisciplinary teams and emphasize care coordination may be necessary to address multiple nondisease-specific problems simultaneously.^{4, 32, 33} Additionally, an approach to medical education that embraces a broader approach to health, recognizes the importance of nondisease-specific problems and prepares physicians to identify patient preferences and goals and incorporate these into treatment strategies will be necessary.^{4, 34} This approach has traditionally been considered part of geriatric medicine and limited to small subset of patients and conditions, however our findings suggest that this approach may be applicable across a wider age spectrum.

While the REGARDS study includes a diverse, U.S. population-based sample, the current analysis has possible and known limitations. Potential nondisease-specific problems, such as urinary incontinence, were not available for the current analysis. Data were not available to account for potential changes in nondisease-specific problems over time. Functional states such as mobility impairment are likely dynamic with transitions between episodes of difficulty and recovery.³⁵ Similarly, in a prior study of community-dwelling older adults who reported exhaustion, nearly half recovered within the following year.³⁶ Although we adjusted for multiple mortality risk factors, there were several co-morbid conditions that are associated with an increased mortality risk, such as chronic obstructive pulmonary disease, cancer and chronic liver disease, that were not collected in the REGARDS study. Confounding due to these conditions could not be addressed. Only brief measures were used for assessing nondisease-specific problems which may have resulted in misclassification. For example, the Six-item Screener of cognitive status does not include measures of executive function, and participants with intact recall and orientation, but poor executive function may be classified as having normal cognition. While data on cognition and depression were obtained by validated measures and polypharmacy was assessed by a pill bottle review during an in-home examination, exhaustion, falls, and impaired mobility were obtained by self-report. Physical performance measures or fall calendars were not available. However, the current study suggests that despite only one-time measures, these brief assessments and self-reported problems were associated with mortality, independent of several mortality risk factors including coronary heart disease, stroke and diabetes. Further, because these measures are brief, busy clinicians may be more likely to evaluate for these problems.

In conclusion, in the current study, nondisease-specific problems including cognitive impairment, depressive symptoms, exhaustion, falls, impaired mobility and polypharmacy were common and associated with mortality among adults across a wide age spectrum. The risk of death was higher with increasing number of these problems. Future studies should determine if evaluating for and modifying these problems will improve survival. Further, research is needed to determine whether innovative healthcare models may be superior to the current system in their capacity to address multiple nondisease-specific problems simultaneously.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of Interest Disclosures: REGARDS was supported by a cooperative agreement (U01 NS041588) with the National Institute of Neurological Disorders and Stroke

C. Barrett Bowling receives support from the NIH (1R03AG042336), the John A. Hart John A. Hartford Foundation/Southeast Center of Excellence in Geriatric Medicine, and the Birmingham/Atlanta GRECC. Monika Safford is employed at the University of Alabama at Birmingham and receives support from NIH, AHRQ, Amgen and consulting in 2012 for diaDEXUS for FDA approval for their lipid assays. Christine Ritchie receives support from the NIH (1K07AG31779-1A1). Virginia G. Wadley receives research support from NIH grants (NO1 HC48047, 2 P30 AG022838-06, R01 AG 039588, R01 NS 061846, 1 R01 AG021958-04, U01 NS51488) and NIH contract HHSN268200900047C, receives grant funding from Genzyme Corporation, has served on an advisory board for Amgen, Inc., and serves on the editorial board of Current Gerontology and Geriatrics Research. None of these affiliations is related to the topic of this paper with the exception of salary support as a REGARDS study investigator (U01 NS51488). Virginia Howard receives support from the NIH (U01 NS041588). Richard M. Allman receives support from the NIH (P30AG031054).

Funding sources: Support was also provided through National Institute on Aging (CBB: R03AG042336-01) and the T. Franklin Williams Scholarship Award (funding provided by: Atlantic Philanthropies, Inc, the John A. Hartford Foundation, the Association of Specialty Professors, the American Society of Nephrology and the American Geriatrics Society). Additional support was provided by the Birmingham/Atlanta GRECC Special Fellowship in Advanced Geriatrics, the John A. Hartford Foundation/Southeast Center of Excellence in Geriatric Medicine in part by the National Institute on Aging (RMA: P30AG031054, HEW: K23 AG032867, P30AG028716).

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Figure 1.
Number of nondisease-specific problems by age group

Figure 2.
Cumulative mortality by number of nondisease-specific problems for participants (a) <65 (b) 65 – 74, (c) ≥ 75 years

Table 1

Baseline characteristics of the REasons for Geographic and Racial Differences in Stroke (REGARDS) study population included in the current analysis by age group^{xx}

	Age Group, years		
	< 65 (n = 12,269)	65 – 74 (n = 7,442)	75 (n = 3,958)
Age	56.9 ± 5.1	69.1 ± 2.8	79.4 ± 3.9
Women	62.4	57.9	56.2
Black	44.1	39.6	35.0
Less than a high school education	8.4	14.4	17.7
Household Income < \$20,000	16.7	22.8	27.3
Geographic Region	36.5	35.1	30.4
Stroke belt	41.0	43.3	50.2
Stroke buckle	22.5	21.7	19.4
Other region	18.8	11.9	6.0
Current smoker	18.8	11.9	6.0
Chronic conditions			
Hypertension	52.1	65.0	68.9
Atrial fibrillation	7.2	9.0	14.1
Coronary heart disease	11.8	20.8	28.1
Stroke	4.5	6.6	9.1
Diabetes mellitus	19.8	24.7	21.4
eGFR < 60 ml/min/1.73 m ²	4.4	13.4	27.1
ACR ≥ 30 mg/g	11.8	15.8	22.4
Physical and Biological Measurements			
Systolic blood pressure (mmHg)	125 ± 16	129 ± 16	131 ± 17
Diastolic blood pressure (mmHg)	77 ± 10	76 ± 9	74 ± 10
Waist circumference (cm)	96.0 ± 16.5	96.1 ± 15.3	93.5 ± 14.7
HDL-cholesterol (mg/dL)	52 ± 16	53 ± 17	53 ± 17
Total cholesterol (mg/dL)	196 ± 40	190 ± 41	185 ± 39
High-sensitivity C-reactive protein(mg/L)	2.3 (0.9–5.5)	2.1 (1.0–4.9)	2.0 (0.9–4.5)
Nondisease-specific problems			
Cognitive impairment	5.1	9.0	14.7
Depressive symptoms	13.6	8.9	9.9
Exhaustion	14.9	11.6	16.3
Falls(≥ 2)	4.6	4.1	5.0
Impaired mobility	15.9	15.8	20.4
Polypharmacy (≥ 10 medications)	14.2	20.8	23.0

Numbers in table are percentage or mean ± standard deviation except for high-sensitivity C-reactive protein which is median (25th–75th quartiles). Stroke buckle = coastal North Carolina, South Carolina, and Georgia. Stroke belt = remainder of North Carolina, South Carolina, and Georgia along with Alabama, Mississippi, Tennessee, Arkansas and Louisiana. Other region = other 40 contiguous U.S. states and Washington DC. eGFR = estimated glomerular filtration rate, ACR = urine albumin-to-creatinine ratio.

Table 2

Age-stratified hazard ratios (95% confidence intervals) for all-cause mortality associated with each nondisease-specific problem

	Age Group, years		
	< 65	65 – 74	75
Age, race, sex, region adjusted hazard ratios (95% CI)			
Nondisease-specific problems			
Cognitive impairment	1.39 (1.01 – 1.90)	1.86 (1.52 – 2.28)	1.53 (1.29 – 1.80)
Depressive symptoms	2.28 (1.86 – 2.80)	1.70 (1.35 – 2.13)	1.46 (1.18 – 1.79)
Exhaustion	2.66 (2.20 – 3.22)	2.26 (1.88 – 2.72)	1.64 (1.40 – 1.93)
Falls (≥ 2 falls)	2.59 (1.86 – 3.62)	2.35 (1.71 – 3.22)	1.85 (1.39 – 2.47)
Impaired mobility	3.66 (3.05 – 4.39)	2.79 (2.36 – 3.28)	2.09 (1.80 – 2.42)
Polypharmacy (≥ 10 medications)	3.01 (2.49 – 3.64)	1.78 (1.51 – 2.10)	1.68 (1.45 – 1.95)
Multivariable adjusted hazard ratios (95% CI)			
Nondisease-specific problems			
Cognitive impairment	1.38 (1.02 – 1.88)	1.44 (1.15 – 1.80)	1.28 (1.06 – 1.54)
Depressive symptoms	1.39 (1.10 – 1.75)	1.03 (0.79 – 1.34)	1.16 (0.92 – 1.47)
Exhaustion	1.43 (1.15 – 1.79)	1.26 (1.02 – 1.55)	1.35 (1.13 – 1.60)
Falls (≥ 2 falls)	1.01 (0.63 – 1.61)	1.50 (1.06 – 2.12)	1.95 (1.44 – 2.64)
Impaired mobility	1.75 (1.42 – 2.17)	1.76 (1.47 – 2.12)*	1.65 (1.39 – 1.95)
Polypharmacy (≥ 10 medications)	1.81 (1.45 – 2.27)	1.13 (0.93 – 1.36)	1.33 (1.13 – 1.57)

Multivariable adjustment includes age, race, sex, education, region of residence, income, current cigarette smoking, atrial fibrillation, coronary heart disease, stroke, diabetes, estimated glomerular filtration rate, albuminuria, systolic and diastolic blood pressure, waist circumference, HDL-cholesterol, total cholesterol, C-reactive protein (log transformed).

* Assumption of proportionality of the hazards was violated for participants 65 to 74 years of age for impaired mobility ($p=0.01$). Multivariable adjusted hazards ratios (95% CI) calculated separately for every two years of follow-up were 2.29 (1.65 – 3.19), 1.79 (1.34 – 2.39), 1.60 (1.14 – 2.25), and 0.95 (0.49 – 1.87) in the first 2 years, 2-4 years, 4-6 years and after 6 years, respectively

Table 3

Age-stratified hazard ratios (95% confidence intervals) for all-cause mortality associated with number of nondisease-specific problems

	Age Group, years		
	< 65	65 – 74	75
Age, race, sex, region adjusted hazard ratios (95% CI) hazard			
Number of nondisease-specific problems			
0	1 (ref)	1 (ref)	1 (ref)
1	2.39 (1.91 – 2.99)	1.95 (1.63 – 2.33)	1.52 (1.29 – 1.80)
2	3.99 (3.12 – 5.12)	3.07 (2.47 – 3.81)	2.71 (2.25 – 3.26)
3	5.84 (4.38 – 7.77)	5.10 (3.85 – 6.74)	3.35 (2.63 – 4.28)
4 - 6	9.16 (6.40 – 13.12)	5.76 (3.91 – 8.49)	3.51 (2.36 – 5.23)
p-trend	<0.001	<0.001	<0.001
For each additional problem	1.79 (1.69 – 1.90)	1.61 (1.52 – 1.71)	1.46 (1.38 – 1.54)
Multivariable adjusted hazard ratios (95% CI)			
Number of nondisease-specific problems			
0	1 (ref)	1 (ref)	1 (ref)
1	1.66 (1.30 – 2.11)	1.49 (1.24 – 1.79)	1.25 (1.05 – 1.49)
2	2.34 (1.78 – 3.08)	1.73 (1.35 – 2.20)	1.90 (1.55 – 2.33)
3	2.35 (1.67 – 3.31)	2.17 (1.57 – 3.00)	2.21 (1.67 – 2.92)
4 - 6	2.92 (1.83 – 4.67)	1.70 (1.06 – 2.73)	2.29 (1.50 – 3.51)
p-trend	<0.001	<0.001	<0.001
For each additional problem	1.34 (1.23 – 1.46)	1.24 (1.15 – 1.34)*	1.30 (1.21 – 1.39)

Multivariable adjustment includes age, race, sex, education, region of residence, income, current cigarette smoking, atrial fibrillation, coronary heart disease, stroke, diabetes, estimated glomerular filtration rate, albuminuria, systolic and diastolic blood pressure, waist circumference, HDL-cholesterol, total cholesterol, C-reactive protein (log transformed).

* Assumption of proportionality of the hazards for each additional geriatric condition among participants 65 to 74 years of age was violated ($p=0.02$). Multivariable adjusted hazards ratios (95% CI) calculated separately for every two years of follow-up were 1.31 (1.15 – 1.49), 1.23 (1.09 – 1.39), 1.24 (1.08 – 1.42), and 1.02 (0.78 – 1.34) in the first 2 years, 2-4 years, 4-6 years and after 6 years, respectively