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Anemia in Old Age Is Associated With Increased Mortality and Hospitalization

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Background. Anemia is common in old age and has been shown to affect older persons' physical function. To more fully understand the detrimental health effects of anemia, we examined the relationship of anemia with death and hospitalization outcomes in a large community-based sample of older persons.

Methods. Data are from 3607 persons, aged 71 years or older, participating in the National Institute on Aging (NIA)-sponsored Established Populations for Epidemiologic Studies of the Elderly (EPESE) study. Anemia was defined according to World Health Organization (WHO) criteria as a hemoglobin concentration below 12 g/dL in women and below 13 g/dL in men. Data on subsequent mortality and hospital admissions over 4 years were obtained from death records and the Medicare database.

Results. Anemia was present in 451 of the 3607 (12.5%) participants. During the follow-up period, anemic persons were more likely to die than were nonanemic persons (37.0% vs 22.1%, $p < .001$). Also, anemic persons were more often hospitalized (65.9% vs 54.6%, $p < .001$) and spent more days in hospital (25.0 vs 13.7, $p < .001$). After adjustment for demographics and baseline comorbidities, anemia significantly predicted subsequent mortality and hospitalization (relative risk = 1.61, 95% confidence interval, 1.34–1.93; and relative risk = 1.27, 95% confidence interval, 1.12–1.45, respectively). After excluding persons with prevalent diseases at baseline, anemia remained significantly associated with increased risks of mortality and hospitalization. A higher hemoglobin level was significantly associated with lower risks of mortality and hospitalization (p for trend $< .001$ for both).

Conclusions. These findings indicate that late-life anemia characterizes persons at risk for important clinical health outcomes, and demonstrate the importance of clinical awareness of anemia even if the person is without apparent clinical disease.

ANEMIA, defined by the World Health Organization (WHO) as a hemoglobin (Hb) concentration below 12 g/dL in women and below 13 g/dL in men (1), is common in old age with a prevalence of approximately 13% in persons aged 70 years or older (2). A majority of the anemia in old age is associated with underlying disease such as cancer, chronic kidney disease, and congestive heart failure (CHF) or due to malnutrition or iron deficiency (3,4). However, in 16%–35% of the cases, it is not possible to directly attribute anemia to these factors (3–5).

Independent of its cause, anemia has been shown to affect physical function among older persons in both cross-sectional as well as longitudinal studies (6,7). These studies have demonstrated that anemia increases the risk of physical disability and is associated with impaired performance and muscle weakness. In disease-specific as well as general older cohorts, anemia increases the risk of mortality (8–10). In addition, two recent independent studies found that, even among persons without anemia, there was a inverse gradient of risk between Hb concentration and outcomes of physical outcomes, with persons having Hb concentrations 0.1–1 g/dL above the anemia cutoff showing significantly more decline than those with higher Hb concentrations (6,11).

To further describe and quantify the clinical outcomes associated with anemia, this cohort study examined subsequent mortality, hospital admissions, and discharge diagnoses among persons with and without anemia as defined by the WHO criteria. In addition, the association between Hb concentration and these clinical outcomes was examined.

Methods

Data for this study are from three communities of the Established Populations for Epidemiologic Studies of the Elderly (EPESE). The sampling design and data collection methods have been described in detail previously (12). More than 10,000 community-dwelling men and women 65 years old or older were interviewed between 1981 and 1983 in East Boston, Massachusetts; New Haven, Connecticut; and Iowa and Washington counties in rural Iowa. Follow-up interviews were conducted annually for 6 years. A total of 5174 persons received a personal in-home interview at the sixth follow-up in 1988. This follow-up assessment is considered the baseline for this study, as this was the first assessment that included blood collection. Because of no available blood sample ($n = 1567$), 3607 persons were included in the present analyses.

Anemia

Using venipuncture, blood was obtained from participants during the present study baseline (1988 assessment). Specimens were sent to a commercial laboratory (Nichols

Institute, San Clemente, CA) where Hb levels were determined using a Coulter counter. Anemia was defined by the WHO criteria (1): Hb concentration below 12 g/dL (7.5 mmol/L) in women and below 13 g/dL (8.1 mmol/L) in men. Analyses were also conducted using Hb as a categorical variable (Hb level $\geq$1 g/dL below anemia cutoff, Hb level 0–0.9 g/dL below anemia cutoff, Hb level 0.1–1 g/dL above anemia cutoff, Hb level 1.1–2 g/dL above anemia cutoff, Hb level 2.1–3 g/dL above anemia cutoff, and Hb level >3 g/dL above anemia cutoff.

Subsequent Mortality and Hospital Admissions

Outcomes for this study included vital status and hospitalizations in the time period from the sixth assessment (baseline for this study) until the end of 1992. Information on vital status came from a seventh follow-up, contacts with proxies, obituaries in local newspapers, and linkage with the National Death Index. Death certificates were coded by a single nosologist using the Ninth Revision of the International Classification of Diseases (ICD-9; 13). Information on date of admission and up to five discharge diagnoses for each participant's hospitalization was gathered from the Health Care Financing Administration (HCFA) Medicare Provider Analysis and Review files which contain information on all persons covered by the Medicare Program Part A (97% of the U.S. population 65 years old or older). Admissions to skilled nursing facilities were not considered hospitalizations for this study. Discharge diagnoses were coded according to the ICD-9, Clinical Modification (13). During follow-up, participants were classified as having either 0 or $\geq$1 hospitalizations. In addition, specific underlying common conditions were considered and divided into various general categories. *Cardiovascular conditions* included acute myocardial infarction (410.0–410.9), angina pectoris (413.0–413.9), CHF (428.0–428.9), and stroke (430.0–432.9, 434, 436). *Gastrointestinal hemorrhage* (578.0–578.9, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533,0, 533.2, 533.4, 533.6) and *cancer* (140.0–212.9) were separately distinguished. *Infectious conditions* included pneumonia (480.0–486.9, 507.0) and other infections (ICD-9, Clinical Modification codes used are available on request). *Other conditions* included diabetes (250.0–250.9), chronic obstructive pulmonary disease (COPD; 490.0–496.9), dementia (290.0–290.9, 294.1, 294.9), decubitus ulcer (707.0), fractures (800.0–819.9, 820.0–822.0, 929.9), and dehydration or electrolytes problems (276.0, 276.5, 276.9).

Covariates

Baseline sociodemographics included age, sex, race, and education. Indicators of baseline health status included smoking status (never, ex-, or current smoker), and body mass index (BMI; weight in kilograms divided by the square of height in meters). Prevalence of coronary heart disease (CHD) was determined by any of the following: (i) discharge diagnosis ICD-9 codes 410–414 in the 3 years before baseline, as ascertained from HCFA Medicare Provider Analysis and Review files; (ii) self-report of heart attack; or (iii) a positive Rose questionnaire (14) for angina at any interview before baseline. Prevalent CHF was identified if participants had a hospital discharge diagnosis in the past 3 years for this disease (ICD-9 code 428) or were currently using diuretic medications and either a digitalis or vasodilator drug. Prevalent diabetes, stroke, cancer, and lung disease were considered present if respondents had ever been told by a doctor that they had these diseases, or if they had a discharge diagnosis in the past 3 years for these diseases (ICD-9 codes 250 for diabetes, 430–434 for stroke, 140–208 for cancer, or 491–493 for lung disease). Infectious diseases were diagnosed by specific hospital discharge diagnoses in the past 3 years (ICD-9 coding available on request). Kidney disease was determined by a serum creatinine level >1.5 mg/dL in women and >1.7 mg/dL in men.

Statistical Analyses

Differences in proportions and means of baseline characteristics and mortality and hospitalization outcomes between persons with and without anemia were assessed using Chi-square and *t* test statistics, respectively. Cox's proportional hazards regression models were used to evaluate the association of anemia with time to death and first hospitalization. Persons surviving with no evidence of hospitalizations or death were censored at the end of the follow-up (December 31, 1992). For the hospitalization outcome, those persons dying with no evidence of hospitalization were censored at the time of their death. Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for the covariates found to be univariately associated with anemia status. Additional Cox's proportional hazards regression analyses were conducted to examine the association between a categorical variable for Hb levels with the mortality and hospitalization outcomes.

Results

The mean age of the total sample at study baseline was 78.2 years (standard deviation [*SD*] = 5.3 years), and 64.4% were female. The mean serum Hb level was 14.5 g/dL (*SD* = 1.6 g/dL) in men and 13.4 g/dL (*SD* = 1.4 g/dL) in women. Anemia was present in 451 of the 3607 (12.5%) participants. Of those persons with anemia, 38 (8.4%) had an Hb level <10 g/dL. As shown in Table 1, participants with anemia were more likely to be older, black, and less educated, and to have a lower BMI and a history of CHD, CHF, diabetes, cancer, infectious disease, or kidney disease compared to those without anemia. In line with this, persons with anemia tended to be hospitalized more often in the prior year. In a multivariate logistic regression analysis, the following baseline characteristics were significantly associated with a higher prevalence of anemia: older age (RR = 1.06, 95% CI, 1.04–1.08), black race (RR = 4.08, 95% CI, 2.74–6.09), BMI (RR = 0.97, 95% CI, 0.96–0.99), cancer (RR = 1.39, 95% CI, 1.08–1.77), kidney disease (RR = 2.75, 95% CI, 2.06–3.68), and hospitalization in the prior year (RR = 1.60, 95% CI, 1.21–2.11).

The mean follow-up period was 4.1 years (*SD* = 1.1 years). During this period, anemic persons were more likely to die (37.0%) than were nonanemic persons (22.1%, $p <$ .001; see Table 2). In addition, the number of persons who were hospitalized during follow-up was significantly higher

Table 1. Baseline Characteristics According to Anemia Status

Characteristics	No Anemia ($N = 3156$)	Anemia ($N = 451$)	p*
Age, mean years (*SD*)	78.0 (5.2)	79.9 (5.8)	<.001
Sex, % female	64.9%	61.0%	.10
Race, % black	6.1%	20.6%	<.001
Smoking status			.07
% Former	27.9%	30.4%	
% Current	8.3%	5.3%	
Years of education, mean (*SD*)	10.1 (3.3)	9.3 (3.4)	<.001
Body mass index	25.1 (6.0)	24.2 (5.8)	.004
Coronary heart disease, %	20.1%	29.0%	<.001
Congestive heart failure, %	9.4%	14.2%	.001
Stroke, %	8.6%	9.8%	.40
Diabetes, %	16.6%	22.6%	.002
Cancer, %	18.6%	24.6%	.002
COPD, %	7.9%	7.1%	.56
Infectious disease, %	5.9%	9.1%	.01
Kidney disease, %	7.0%	20.1%	<.001
Hospitalization past year, %	13.2%	22.2%	<.001

Notes: *p value based on chi-square analyses (categorical variables) and t test analyses (continuous variables).

SD = standard deviation; COPD = chronic obstructive pulmonary disease.

among those with anemia (65.9%) than among those without anemia (54.6%, $p < .001$). Anemic persons had significantly more and longer hospital stays during follow-up than did nonanemic persons.

Table 3 gives a description of the subsequent hospital discharge diagnoses among persons with and without anemia. During follow-up, anemia was significantly associated with a variety of hospital discharge diagnoses: cardiovascular conditions (especially angina and CHF), gastrointestinal hemorrhage, cancer, infectious conditions, diabetes, and decubitus ulcer. Nonsignificant trends were found for an increased occurrence of hospitalizations for fractures and dehydration with anemia.

Table 4 shows risks for mortality and hospitalization after adjustment for baseline characteristics with (borderline) significant univariate associations with anemia: age, sex, race, education, smoking status, BMI, CHD, CHF, diabetes, cancer, infectious disease, kidney disease, and hospitalization in past year. Anemia significantly increased the risk of

Table 2. Subsequent Hospitalization and Mortality Information According to Anemia Status

Hospitalization/ Mortality Variable	No Anemia ($N = 3156$)	Anemia ($N = 451$)	p*
Mean years of follow-up (*SD*)	4.1 (1.0)	3.6 (1.3)	<.001
Died during follow-up, %	22.1%	37.0%	<.001
Hospitalized during follow-up, %	54.6%	65.9%	<.001
No. of hospitalizations during follow-up (*SD*)	1.4 (2.0)	2.0 (2.5)	<.001
No. of hospital days during follow-up (*SD*)	13.7 (28.1)	25.0 (47.3)	<.001
No. of hospital days per hospitalization (*SD*)	9.2 (9.6)	10.9 (10.4)	.01

Notes: *p value based on chi-square tests (categorical variables) and t test analyses of (continuous variables).

SD = standard deviation.

Table 3. Hospital Discharge Diagnoses During Follow-Up According to Anemia Status

	No Anemia ($N = 3156$)		Anemia ($N = 451$)		
Discharge Diagnoses	*N*	%	*N*	%	p
Cardiovascular conditions	768	24.3	145	32.2	<.001
Acute myocardial infarction	224	7.1	38	8.4	.31
Angina	180	5.7	37	8.2	.04
Congestive heart failure	432	13.7	101	22.4	<.001
Stroke	219	6.9	34	7.5	.64
Gastrointestinal hemorrhage	144	4.6	40	8.9	<.001
Cancer	313	9.9	74	16.4	<.001
Infectious diseases	539	17.1	120	26.6	<.001
Pneumonia	305	9.7	61	13.5	.01
Acute and chronic infections	330	10.5	85	18.8	<.001
Other conditions					
Diabetes	324	10.3	60	13.3	.05
COPD	320	10.1	47	10.4	.85
Dehydration	285	9.0	50	11.1	.16
Fractures	249	7.9	45	10.0	.13
Dementia	79	2.5	12	2.7	.84
Decubitus ulcer	27	0.9	9	2.0	.02

Note: COPD = chronic obstructive pulmonary disease.

mortality (RR = 1.63, 95% CI, 1.37–1.95) and the risk of hospitalization (RR = 1.23, 95% CI, 1.09–1.41). After excluding persons with important baseline conditions (CHD, CHF, diabetes, stroke, cancer, lung disease, kidney disease, and infectious disease), the association between anemia and mortality and hospitalization outcomes was very similar, if not higher: RR for mortality = 2.12 (95% CI, 1.48–3.04) and RR for hospitalization = 1.30 (95% CI,

Table 4. Adjusted Risk of Mortality and Hospitalization According to Anemia Status*

		Mortality		Hospitalization	
	N	Adjusted RR (95% CI)	p	Adjusted RR (95% CI)	p
Total sample					
No anemia	3156	1		1	
Anemia	451	1.63 (1.37–1.95)	<.001	1.23 (1.09–1.41)	.001
Persons without baseline diseases†					
No anemia	1396	1		1	
Anemia	142	2.12 (1.48–3.04)	<.001	1.30 (1.02–1.66)	.03
Persons with baseline diseases†					
No anemia	1760	1		1	
Anemia	309	1.43 (1.16–1.76)	.001	1.21 (1.04–1.41)	.01
Events in the first 2 y of follow-up					
No anemia	3156	1		1	
Anemia	451	1.63 (1.23–2.17)	.001	1.26 (1.07–1.50)	.007
Events after the first 2 y of follow-up					
No anemia	3156	1		1	
Anemia	451	1.51 (1.19–1.92)	.001	1.20 (0.98–1.46)	.08

Notes: *Adjusted for age, sex, race, education, smoking status, body mass index, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease, and hospitalization in past year.

†Baseline diseases are coronary heart disease, chronic heart failure, diabetes, stroke, cancer, infectious disease, lung disease, and kidney disease.

RR = relative risk; CI = confidence interval.

1.02–1.66). The association between anemia and mortality and hospitalization outcomes was also significantly present among persons with one or more of these baseline conditions. Additional analyses stratified for follow-up duration ($\leq$2 years or >2 years), showed that the association between anemia and clinical outcomes was not just present in the first 2 years of follow-up but remained similarly effective in subsequent years of follow-up.

Finally, we calculated adjusted risk of mortality and hospitalization according to increasing categorical Hb levels: Hb $\geq$1 g/dL below anemia cutoff (n = 159), Hb 0–0.9 g/dL below anemia cutoff (n = 292), Hb 0.1–1 g/dL above anemia cutoff (n = 736), Hb 1.1–2 g/dL above anemia cutoff (n = 1109), Hb 2.1–3 g/dL above anemia cutoff (n = 820), and Hb $\geq$3.1 g/dL above anemia cutoff (n = 491) (see Figure 1). After adjustment for covariates, a higher Hb level was significantly associated with a lower risk of mortality (p for trend < .001) and a lower risk of hospitalization (p for trend = .004). Compared to persons with a Hb level of 1.1–2 g/dL above the anemia cutoff (reference group), persons with Hb levels of 0–0.9 g/dL or $\geq$1 g/dL below the anemia cutoff had an increased mortality risk of 1.66 (95% CI, 1.30–2.12) and 1.91 (95% CI, 1.44–2.53), respectively. It is interesting that persons with a Hb level of 0.1–1 g/dL above the anemia cutoff also differed significantly from those with a Hb level of 1.1–2 g/dL above the anemia cutoff (RR = 1.32, 95% CI, 1.08–1.60). Regarding hospitalizations, persons with Hb levels of 0–0.9 g/dL or $\geq$1 g/dL below the anemia cutoff had an increased risk of 1.15 (95% CI, 0.97–1.36) and 1.47 (95% CI, 1.20–1.80), respectively, compared to the reference group.

Discussion

In our study, anemia defined according to the WHO criteria was found to be significantly associated with increased mortality and hospitalizations. These associations remained significant after adjustment for age, gender, BMI, and various comorbid conditions, and were confirmed among persons without measured prevalent diseases at baseline. Hospital discharge diagnoses that occurred more in anemic persons were for cancer, infectious disease, cardiovascular disease, diabetes, and decubitus ulcers. In addition, we found a significant inverse gradient of risk between Hb concentration and subsequent mortality and hospitalization events. Our findings are in line with prior findings by Chaves and colleagues (9) and Izaks and colleagues (8) that reported an inverse gradient of risk between Hb level and mortality among older women and among a sample of persons 85 years old or older.

Our study confirms that anemia is common among older persons. Twelve percent of the men and women in our older sample fulfilled the WHO criteria for anemia. This percentage is consistent with other reported prevalences of 11% in persons 65 years old or older (5), and 13% in persons 70 years old or older (2). In both univariate and multivariate analyses, older age was a significant determinant of anemia, clearly indicating that the prevalence of anemia increases with age. Of the persons 85 years old or older, 20% had anemia, which is in line with reported prevalences in other studies of the oldest old (8,15). Other significant independent determinants of anemia were diabetes, cancer, kidney disease, and hospitalization in the prior year. These results reflect that certain underlying chronic diseases are likely to explain a large part of the anemia prevalence. Previous studies indicate that, in addition to underlying disease, malnutrition and iron, folate, and vitamin B12 deficiencies alone or in combination may explain another 20%–30% of the anemia cases. However, in about 16%–35% of cases, it is not possible to attribute anemia to underlying factors (3–5). The latter could partly be due to unidentified underlying conditions, reduced bone marrow reserve, adaptation to a reduced lean body mass with diminished oxygen requirements, or reduced erythropoietin secretion (16,17).

A major question regarding anemia in older persons is whether anemia is an independent risk factor for functional decline or is merely a surrogate marker of coexistent chronic diseases or the aging process itself. The fact that no substantial differences were observed between results in the overall sample and those in a disease-free sample suggests that the effect of anemia on clinical outcomes is independent of chronic or acute disease status. Alternatively, it is possible that there may be a direct, adverse effect of anemia that explains the higher occurrence of clinical outcomes. Physiologically, the cardiovascular and pulmonary impairments that are common in older people can substantially limit the effectiveness of compensatory responses to low Hb concentrations. In this context, even low-normal Hb concentrations could cause reduced oxygen delivery and contribute to the development of adverse clinical outcomes and subsequent hospitalizations and mortality.

Although anemia may have a direct physiological impact, it is also likely that part of our findings are due to the fact that anemia represents underlying disease. Our analyses were adjusted for common chronic conditions, and results were confirmed in analyses that excluded persons with diseases commonly linked to anemia. Still, anemia could reflect disease severity, subclinical diseases, or other diseases not measured (e.g., liver and/or pancreatic disease). In this context, anemia appears to be an effective prognostic marker for poorer health outcomes and merits further clinical investigation.

During the 4-year follow-up period, anemic older persons were more likely to be hospitalized for cancer, infectious disease, cardiovascular disease (e.g., CHF and angina), diabetes, and decubitus ulcers, with a trend toward increased hospitalizations for fractures. These findings confirm that anemia is linked with certain diseases such as cancer and CHF, and that, over time, hospitalizations for these conditions are more likely. In addition, some other hospitalization discharge diagnoses that were more common among anemic older persons were decubitus ulcers, fractures, and infections, which could be considered more general conditions indicative of frailty (18). These findings suggest that anemia, rather independent of a certain disease, may identify frail older persons. This suggestion is consistent with recent findings in which a low Hb level is associated with frailty (19,20) and with increased disability, poorer physical performance, and lower muscle strength (6,7).

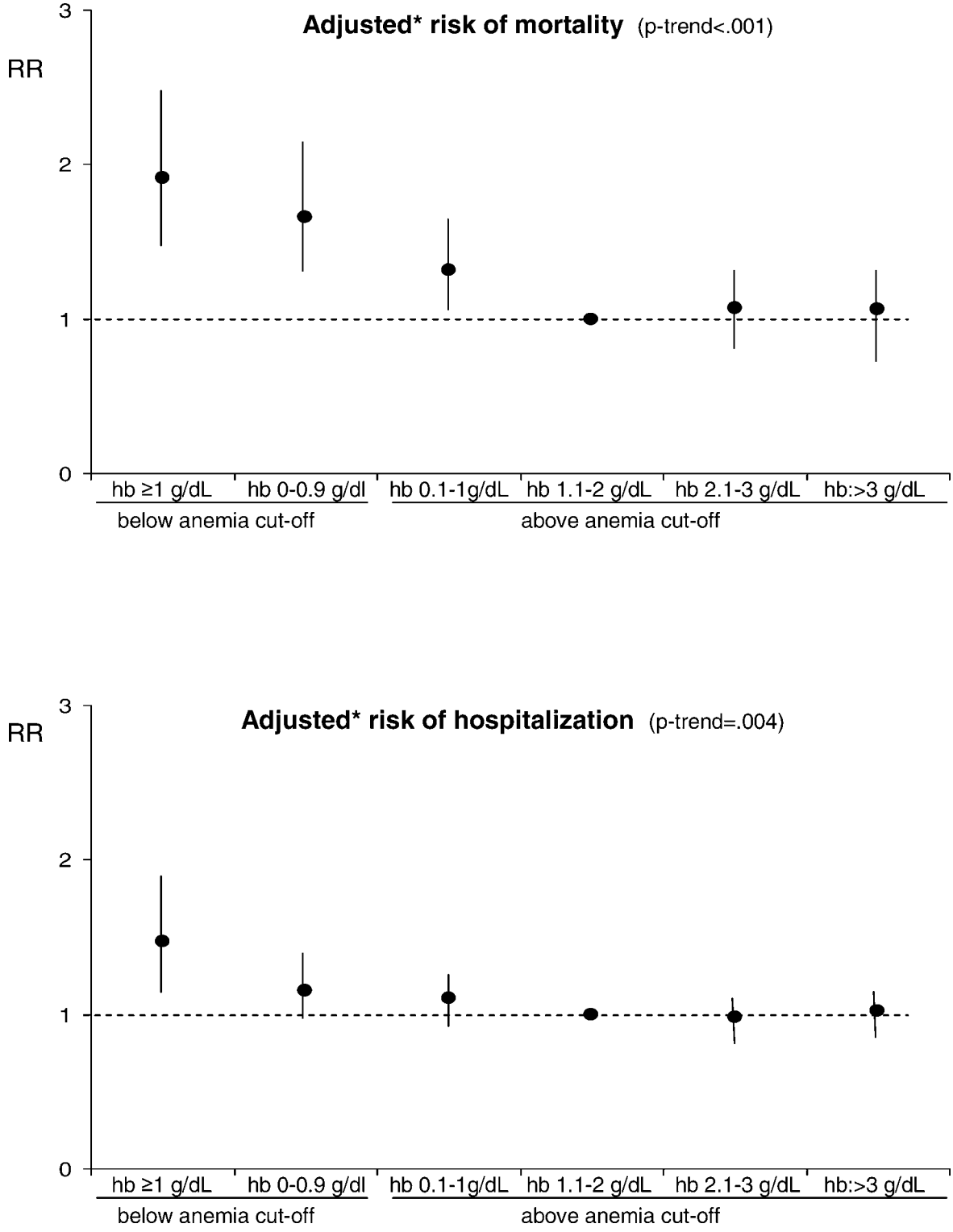

Figure 1. Adjusted risks (RRs) of mortality and hospitalization according to hemoglobin (hb) levels. *Adjusted for age, sex, race, education, smoking status, body mass index, coronary heart disease, congestive heart failure, diabetes, cancer, infectious disease, kidney disease, and hospitalization in past year.

Our findings indicate a significant inverse gradient of risk between Hb concentration and subsequent mortality and hospitalization events. Even among the nonanemic persons, those with low-normal Hb levels (0.1–1 mg/dL above the anemia cutoff) were at higher risk of death than those with higher Hb levels. These findings are consistent with earlier findings that low-normal Hb levels are associated with increased risks for disability and physical decline (11). It

could be that a large proportion of persons with low-normal Hb developed anemia shortly after the baseline examination, which could explain their increased risk of mortality. It could be, however, that low-normal Hb levels already identify persons at risk for certain clinical outcomes. Further research is needed to explore these issues, as this will provide insight into whether it is appropriate to adjust the WHO anemia criteria in old age. In summary, our findings show that, because of the increased risks of mortality and hospitalization, Hb levels below normal in older persons are a reason for clinical awareness, even if older persons have no apparent clinical disease.

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