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ORIGINAL ARTICLE

Anemia and mortality in older persons: does the type of anemia affect survival?

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Abstract Anemia is a common condition among community-dwelling older adults. The present study investigates the effect of type of anemia on subsequent mortality. We analyzed data from participants of the Third National Health and Nutrition Survey who were aged ≥50 and had valid hemoglobin levels determined by laboratory measurement. Anemia was defined by World Health Organization criteria. 7,171 subjects met our inclusion criterion. Of those with anemia ($n = 862$, deaths = 491), 24% had nutritional anemia, 11% had anemia of chronic renal disease, 26% had anemia of chronic inflammation, and 39% had unexplained anemia. We found an overall relative risk (RR) for mortality of 1.8 ($p < 0.001$) comparing those with anemia to those without, after adjusting for age, sex, and race. After we controlled for a number of chronic medical conditions, the overall RR was 1.6. Compared to persons without anemia, we found the following RRs for the type of anemia: nutritional (2.34, $p < 0.0001$), chronic renal disease (1.70, $p < 0.0001$), chronic inflammation (1.48, $p < 0.0001$), and unexplained (1.26, $p < 0.01$). Anemia is common although not severe in older non-institutionalized adults. When compared with non-anemic older adults, those with nutritional anemia or anemia due to chronic renal disease have the highest mortality risk.

Keywords Life expectancy · Survival · Relative risk

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Introduction

Anemia is a common condition among community-dwelling older adults; the prevalence increases with age, beginning at about age 50, and reaching approximately 20% at ages 85 and older [1]. For many years, anemia in older persons was not considered a serious clinical condition by many physicians. It was instead thought to be either an insignificant finding in an otherwise healthy patient, or a comorbidity that compounded the complexity of managing a patient with other disease [2]. Although, it was previously believed that declines in hemoglobin levels might be a normal consequence of aging, evidence has accumulated that anemia reflects poor health and increased vulnerability to poor outcomes in older persons [3, 4]. The question of whether aging (as opposed to disease) causes anemia has recently become more relevant, given the possibility of treatment without blood transfusion.

Anemia has been shown to be associated with functional decline and frailty, even in the absence of concomitant illness [5, 6]. It has been identified as an independent predictor of survival after adjustment for age, sex, and confounding factors [7–12]. The severity of anemia affects survival, and a J-shaped relationship has been documented [4, 10, 11]. Its effect has been studied in general [7–15], in the very old [16], and in subgroups of persons with heart failure [17–24] or on dialysis [25–27].

In clinical practice, many different types of anemia exist, with many causes and manifestations. Several schemes have been proposed to categorize anemias by etiology. None of these is entirely satisfactory because within each classification the various subdivisions are not completely inclusive [33]. Data from population-based epidemiological surveys on older adults have established that there are three broad types of anemia, which occur

with nearly equal frequency [1, 11, 15, 34, 35]. These are: (1) anemia due to nutritional deficiencies or blood loss, (2) anemia associated with chronic illness or chronic inflammation, and (3) unexplained anemia. These three types of anemia arise from a variety of causes, most are common to all age groups, but some are more characteristic of aging versus younger populations [36].

Nutrient-deficiency anemias can be due to dietary lack, malabsorption, or blood loss. Lack of nutrients, such as iron, B_{12}, or folate is a common cause of anemia in older adults. Iron deficiency anemia is the most common form and is usually associated with chronic gastrointestinal blood loss. Vitamin B_{12} deficiency as defined by biochemical criteria is common in older adults but anemia due to B_{12} deficiency is not. Folate deficiency used to be common in older adults. Fortification of national diets and an increase in the use of folate supplements by older adults have made this form of nutritional anemia less common [3, 37–39].

The anemia of chronic illness appears to be primarily related to inflammation and is increasingly referred to as the "anemia of chronic inflammation". This type of anemia usually develops in the presence of disorders such as chronic infections, malignancy, autoimmune and inflammatory disorders [3, 37, 40]. Although this is the prevailing opinion, some investigators have hypothesized that this type of anemia is a beneficial and adaptive response to an underlying disease state [40].

The anemia seen in chronic kidney disease is also common in older adults, since kidney function declines with age. This type of anemia is now understood to be at least to some degree separate from the anemia of chronic inflammation/chronic disease. The primary cause of anemia in chronic kidney disease is a decline in the renal production of erythropoietin. A shortened red blood cell lifespan and suppressed red blood cell production as well as increased pro-inflammatory cytokines that occur in chronic kidney disease, may also contribute to the pathogenesis of anemia in this population [37, 41].

The underlying cause of anemia fails to be identified in a significant proportion of older adults. Whether unexplained anemia represents a spectrum of undiagnosed etiologies or has a unifying pathogenesis remains unclear. Possible age-related explanations include a blunted erythropoietic response in the setting of iron deficiency, higher circulating levels of pro-inflammatory cytokines, decreased androgen levels and decreased erythropoietic reserve due to a decreased proliferative and regenerative capacity of bone marrow stem cells. In some cases, inadequate evaluation may have prevented the recognition of the common forms of anemia such as those mentioned above. In addition, although not a concomitant of normal aging, early cases of myelodysplastic syndrome, an age-dependent malignant stem cell disorder, which is more common in older adults, is associated with reduced life expectancy and may go undetected in an epidemiological survey [1, 42, 43].

Whether the type of anemia significantly affects survival has not received much attention. To our knowledge, the only information currently available comes from the Women's Health and Aging Study I, a population-based study of anemia in moderately-severely disabled women living in the community in Baltimore, Maryland [15]. In that study, women with anemia and renal disease (HR 1.99, 95% CI 1.18–3.35, $p = 0.009$), anemia of chronic inflammation (HR 1.69, 95% CI 1.00–2.84, $p = 0.05$), and unexplained anemia (HR 1.32, 95% CI 0.80–2.19, $p = 0.28$) had a higher risk of death than those without anemia, and those with nutritional deficiencies actually had a lower risk (HR 0.79, 95% CI 0.29–2.14, $p = 0.64$).

The present study, based on analysis of the NHANES III data, further investigates the effect of type of anemia on subsequent mortality. We quantify the effect in both the entire database and in a subset of persons free of prevalent disease at baseline.

Methods

Our data was from the Third National Health and Nutrition Survey (NHANES III). This has been described in detail elsewhere [28]. In brief, the survey was conducted on a nationwide probability sample of approximately 34,000 persons aged 2 months and older. It was designed to obtain nationally representative information on the health and nutritional status of the population of the United States through interviews and direct physical examinations. A full assessment included a home interview, an examination, and laboratory tests including hemoglobin measurement, either in a mobile examination center or at home. Persons were enrolled from 1988 to 1994. Follow-up was through December 31, 2000. Vital status was determined using the National Death Index.

We restricted attention to those aged 50 and over who had valid hemoglobin levels determined by laboratory measurement. There were 7,173 such persons. Two were lost to follow-up, leaving a sample size of 7,171. These persons were followed for a maximum of 12.2 years (average 7.7 ± 2.9 years), over which time there were 2,365 deaths.

We used age 50 for two reasons: (1) the prevalence of anemia is known to increase with age, beginning at roughly age 50, and (2) we also wanted to study a healthy subset (defined below) who had no major medical conditions other than anemia, which required an age much younger than 65 in order to have a sufficient sample size.

Persons with low hemoglobin concentration at baseline were considered anemic. We used the WHO definition of anemia: a hemoglobin concentration <130 g/L in men and <120 g/L in women [29]. Various other definitions have been used [6, 14]. Questions have been raised as to the validity of the WHO definition of anemia for an elderly population [11, 30]. However, there is no other universally accepted definition of anemia and we thus opted to rely on the WHO definition here.

Mild anemia was further defined as a hemoglobin concentration of 100–130 g/L in men and 100–120 g/L in women. Moderate and worse anemia was defined as any hemoglobin concentration below that of mild anemia. To determine the type of anemia, we used the criteria of Guralnik et al. [1]:

1. Nutritional deficiency anemia was based on iron, vitamin B_{12}, or folate deficiency.
   a. Iron deficiency was considered present if the subject had at least two of the following three criteria: transferrin saturation rate less than 15%, serum ferritin concentration less than 12 ng/mL, and erythrocyte protoporphyrin concentration greater than 1.24 μM.
   b. Vitamin B_{12} deficiency was defined as serum B_{12} concentration less than 200 pg/mL.
   c. Folate deficiency was defined as red blood cell (RBC) folate concentration less than 102.6 ng/mL. In those who underwent home examination only, folate deficiency was defined as serum folate concentration less than 2.6 ng/mL.
2. If there was no evidence of nutritional anemia, subjects with anemia were classified as having anemia of chronic renal disease if they had an estimated creatinine clearance of less than 30 mL/min.
3. If there was no nutritional anemia or anemia of chronic renal disease, then those subjects who had a serum iron count of less than 60 μg/dL without evidence of iron deficiency were considered to have anemia of chronic inflammation (ACI). Note: ACI was previously known as anemia of chronic disease as it was initially thought to be associated primarily with infectious, inflammatory, or neoplastic disease. However, studies have shown that ACI can be seen in a variety of conditions, including severe trauma, heart failure, diabetes mellitus, and in those with acute or chronic immune activation. The change was made to more accurately portray the role of inflammation in this type of anemia.
4. Otherwise, subjects with anemia were considered to have unexplained anemia.

Information on six comorbidities (CHF, stroke, MI, cancer, diabetes, and hypertension) came from response to questionnaires asking if any doctor had ever diagnosed the patient with the given condition. We did not have a severity scale for these conditions. COPD was based on spirometry data, defined as FEV1/FVC less than 0.70. Renal insufficiency was based on serum creatinine measurement, defined as estimated GFR less than 60. Overall, anemia was very weakly correlated ($r < 0.10$) with all of these conditions except renal insufficiency ($r = 0.18$).

Analyses were performed using the statistical package SAS 9.1 for Windows [31]. Cox proportional hazards regression models [32] were developed using the "PROC PHREG" procedure in SAS. The models included adjustments for age, sex, race, smoking status, BMI, the medical conditions listed in Table 2, and type of anemia.

We also defined a subset of persons who at baseline had no chronic medical conditions, no history of smoking, and no obesity or underweight (henceforth referred to this as the "healthy subset"), and determined the effects of anemia in this group.

Results

There were 7,171 subjects from NHANES III who met our inclusion criterion. Table 1 shows the demographic characteristics, stratified by presence of anemia at baseline. As can be seen, persons with anemia tended to be older (average age 73 cf. 68, $p < 0.01$), non-white (41% cf. 21%), and have more medical conditions (especially renal insufficiency) than their non-anemic counterparts do.

Of the 862 persons with anemia, 793 (92%) had mild anemia, and 69 (8%) had moderate or severe. Because the vast majority had the mild form, and our emphasis here was on type of anemia rather than on the severity, we considered excluding those with moderate or severe anemia. Such exclusion, however, did not significantly change the findings. We therefore report here the findings for the entire data set.

Of those with anemia, 24% had nutritional anemia, 11% had anemia of chronic renal disease, 26% had anemia of chronic inflammation, and 39% had unexplained anemia. Table 2 further describes this group. The group with anemia of chronic renal disease was significantly older (average age 78 cf. 73, 71, and 72; $p < 0.01$ in all cases), and had the highest percentage of females (though this was not statistically significant). Those with anemia of chronic inflammation or unexplained anemia were much less likely to have moderate or severe anemia (only 2% did, cf. 19 and 16% in the other two groups).

In analyses of the effect of anemia on mortality, we found an overall RR of 1.8 ($p < 0.001$) comparing those with anemia to those without, after adjusting for age, sex, and race. We also found an RR of 2.4 ($p < 0.001$) for

Table 1 Demographics of persons age 50 and over in NHANES III

	Non-anemic	Anemic
n	6,309	862
Deaths	1,874	491
Age	68 ± 11	73 ± 11
Male	48	49
Female	52	51
White	79	59
Non-white	21	41
Underweight	3	5
Satisfactory weight	31	40
Overweight	39	36
Obese	27	19
Smoker	21	16
Former smoker	42	42
Never smoker	37	42
CHF	7	11
Stroke	6	10
MI	10	12
COPD	38	48
Cancer	7	12
Diabetes	14	21
HTN	42	49
Renal insufficiency	11	31
Anemia severity		
Mild	–	92
Moderate/severe	–	8
Anemia type		
Nutritional	–	24
Chronic renal		11
Chronic inflammation	–	26
Unexplained	–	39

All figures are column percentages except for *n*, deaths, and age (mean ± standard deviation)

moderate or severe anemia, and 1.5 ($p < 0.001$) for mild anemia, both compared with no anemia. We then additionally controlled for the medical conditions listed in Tables 1 and 2 (by adding these to the original Cox Model). The overall RR for anemia was 1.6, slightly attenuated from the above 1.8. This RR did not appear to vary by sex. It did, however, vary with age. In separate analyses by age group, we found the following RRs: ages 50–59, 2.89; 60–69, 2.13; 70–79, 1.52; 80+, 1.34). That is, we observed the typical pattern of a decreasing RR with age.

We then turned attention to the effect of type of anemia. We did not stratify by severity or age. We did, however, as above, control for age, sex, and the medical conditions listed in Tables 1 and 2. Table 3 shows the results. We found the following RRs (compared to persons without anemia): nutritional anemia (2.34, $p < 0.0001$), anemia of chronic renal disease (1.70, $p < 0.0001$), anemia of chronic inflammation (1.48, $p < 0.0001$), unexplained anemia (1.26, $p < 0.01$). The first two types were statistically different from the unexplained type ($p < 0.01$), but ACI was not statistically different from the unexplained type ($p > 0.05$). This latter finding may reflect the observation by Ferrucci et al. [45] that in both ACI and unexplained anemia in older persons there is an increase in pro-inflammatory cytokines associated with a similar stepwise decrease in erythropoietin levels.

In the healthy subset ($n = 853$, deaths = 97)—after accounting for age, race, and sex—the RR of mortality for persons with anemia ($n = 65$, any type) was 1.45 (95% CI 0.82–2.54) compared to those without anemia ($n = 788$). There was not sufficient data to test for a severity effect. In analyses concerning type, we found the following RRs: nutritional anemia (1.35, $p = 0.52$; $n = 19$), anemia of chronic renal disease (6.74, $p = 0.06$; $n = 16$), ACI (2.62, $p = 0.11$; $n = 15$), and unexplained anemia (1.11, $p = 0.81$; $n = 15$), all compared with those who did not have anemia. These varied from the corresponding values in Table 3, though none was statistically different from 1.00, and they did not statistically differ from one another. This lack of statistical significant was undoubtedly due to the small sample sizes in this subset.

Discussion

It is well known that anemia is associated with increased mortality. Some of the more recent and relevant studies are outlined in Table 4. The overall RR reported here (1.8) is seen to be consistent with this literature. The effect of anemia on mortality depends upon the severity, as documented here (RRs of 2.4 for the moderate/severe group, and 1.5 for the mild group). Again, this is consistent with the literature.

The RR for our healthy population (1.45) is rather smaller than the only analogous figure we could find in the literature: Penninx et al. [9] reported an RR of 2.12 in a subset who did not have prevalent disease at baseline. That our figure (1.45) is significantly less than theirs (2.12) is surprising, because our overall RR (1.8) is modestly larger than theirs (1.63). Further, their overall study population (that is, without any exclusions) appeared to be quite similar to ours, except for age (theirs was older, which would not explain their higher RR). It may be, however, that the lower RR given here is due to the small sample size and consequent large standard error of the estimate.

Most cross-sectional and longitudinal studies have shown that average hemoglobin levels do not change significantly in healthy older adults aged between 60 and 98. However, the prevalence and incidence of anemia does

Table 2 Demographics of the 862 persons age 50 and over in NHANES III who have anemia as defined here

	Nutritional	Chronic renal	Chronic inflammation	Unexplained
n	206	92	225	339
Deaths	129	74	120	168
Age	73 ± 12	78 ± 10	71 ± 11	72 ± 11
Male	44	38	54	53
Female	56	62	46	47
White	71	60	51	56
Non-white	29	40	49	44
Underweight	5	4	4	6
Satisfactory weight	39	39	43	41
Overweight	35	40	33	36
Obese	21	17	20	17
Smoker	17	11	18	16
Former Smoker	38	40	41	46
Never smoker	45	49	41	38
CHF	12	20	10	9
Stroke	8	14	12	9
MI	15	16	11	10
COPD	47	49	50	46
Cancer	14	9	9	14
Diabetes	19	36	23	17
HTN	47	60	49	46
Renal insufficiency	30	96	19	22
Anemia severity				
Mild	81	84	98	98
Moderate/severe	19	16	2	2

All figures are column percentages except for *n*, deaths, and age (mean ± standard deviation)

increase with age, suggesting that anemia in older adults may be due to the increased prevalence of comorbidity and underlying chronic inflammation in this population [44]. This may explain the association between the different types of anemia and the RRs, we found in our age-, sex- and comorbidity-adjusted analysis. When compared with non-anemic older adults, those with nutritional anemia had the highest risk, followed by those with anemia of chronic kidney disease, anemia associated with chronic inflammation/chronic illness, and unexplained anemia.

Iron deficiency anemia alone or in combination with vitamin B_{12} and/or folate deficiency, constitute more than half of the nutritional anemias seen in older adults [3]. In industrialized countries, iron deficiency is rarely the result of dietary deficiency. It is most often the result of chronic gastrointestinal blood loss caused by esophagitis, gastritis, ulcer (related or not related to nonsteroidal anti-inflammatory drug intake), and malignancy. Although the statistical analysis (based on prevalent comorbidity) suggests that nutritional anemia is an independent predictor of mortality, gastrointestinal blood loss and its causes are often occult [38]. Most anemias in older adults are mild and are not associated with cardiac dysfunction. Those with nutritional anemia were more likely to have moderate/severe anemia, which if extended for a long period, may result in ventricular and arterial remodeling and cardiac dysfunction; and may produce sufficient hypoxia to aggravate underlying cardiovascular and pulmonary disorders [19, 43]. However, exclusion of moderate/severe anemia patients from the analysis did not significantly change the findings.

In chronic kidney disease, there is a clear linear relationship between the prevalence of anemia and kidney function; anemia increases with declining kidney function. Impaired erythropoietin production appears not be clinically relevant until creatinine clearance is <30 mL/min. There are several potential explanations for the increased mortality risk associated with the anemia of chronic kidney disease. In addition to having an increased likelihood of moderate/severe anemia, people with chronic kidney disease were older and had a higher prevalence of hypertension, congestive heart failure, and diabetes. This implies a higher likelihood of damage to one or more other organs, including the heart. These patients may have microvascular and/or macrovascular disease of the coronary circulation or left ventricular hypertrophy and therefore be more susceptible to ischemia induced by anemia [11, 37, 41].

As older adults often suffer from multiple comorbidities, it is not surprising that chronic inflammation/chronic

Table 3 Multivariate mortality model

Factor	Hazard ratio	*p* value
Male	1.29	<0.01
White	0.99	0.81
Ages 50–59	1.00	Reference
Ages 60–69	1.95	<0.01
Ages 70–79	3.80	<0.01
Ages 80+	9.00	<0.01
Underweight	1.82	<0.01
Satisfactory weight	1.00	Reference
Overweight	0.86	<0.01
Obese	0.83	<0.01
Smoker	1.50	<0.01
Former smoker	1.15	<0.01
Never smoker	1.00	Reference
CHF	1.51	<0.01
Stroke	1.51	<0.01
MI	1.25	<0.01
COPD	1.32	<0.01
Cancer	1.33	<0.01
Diabetes	1.65	<0.01
Hypertension	1.10	0.03
Renal insufficiency	1.48	<0.01
Anemia type		
Nutritional	2.34	<0.01
Chronic renal	1.70	<0.01
Chronic inflammation	1.48	<0.01
Unexplained	1.26	<0.01
None	1.00	Reference

illness is a common cause of anemia. It is also common for this type of anemia to occur in the presence of other causes of anemia, including iron deficiency. Although specific laboratory criteria for this type of anemia have been proposed, they are frequently not used and this type of anemia often occurs as a diagnosis of exclusion especially when anemia develops in the presence of one or more chronic medical problems [37]. This type of anemia tends to be mild and the severity of the anemia generally correlates with the severity of the underlying disease. In the NHANES III survey, the prevalence of moderate/severe anemia was considerably lower in patients with chronic inflammation/chronic illness anemia than seen in patients with nutritional–deficiency anemia and the anemia of chronic kidney disease [1].

Unexplained anemia appears more commonly with advancing age and is rarely, if ever, encountered in younger adults. Case definitions used to classify types of anemia in an epidemiological study cannot be regarded, strictly speaking, as diagnostic and may not be the same as the ordinary clinical definitions. In the NHANES III survey, the determinations concerning etiology were based upon laboratory data alone without an accompanying clinical definition. Because older adults often have several associated comorbid conditions and are commonly taking a variety of medications, some of which may contribute to anemia, the etiology of anemia is frequently difficult to determine, even after extensive investigations, including bone marrow examination. Even with the advent of better tests such as serum ferritin, methylmalonic acid, soluble transferrin receptor, a significant portion of older persons with anemia will be diagnosed as having unexplained anemia. In the NHANES III survey, the prevalence of moderate/severe anemia was considerably lower in patients with unexplained anemia than seen in patients with nutritional-deficiency anemia and the anemia of chronic kidney disease [1].

To further evaluate the relationship between anemia type and mortality, it would be helpful to examine the multiple causes of death in each case, and compare patterns amongst the types of anemia. This is beyond the scope of the present study.

Our results differ from those of Semba [15]. Notably, we found the highest RR in those with nutritional anemia, whereas in their study it was the lowest (2.34 cf. 0.79). This wide variance may be due to random variation, as their subgroup was based on a very small sample size ($n = 22$) and apparently only four deaths. Further, our RRs for the other conditions were modestly lower than theirs. This would be expected, as we controlled for many concomitant medical conditions while they did not. On the other hand, their baseline population was disabled, thus having higher initial risk, so their resulting RRs would be expected to be lower than ours (analogous to why the RR is smaller in older populations than in younger).

A limitation of the present study is that in the NHANES III data there were insufficient people without medical or other conditions (other than anemia) to sufficiently determine whether the type of anemia was statistically significantly associated with survival in otherwise healthy people. Another limitation is that anemia was defined using a single set of lab values, rather than repeated measurements over time; it is therefore not known if the low levels of hemoglobin represented a chronic condition or an acute one. A final limitation is that we did not have sufficient data to investigate separately the various subtypes of nutritional deficiency anemia (iron, B_{12}, and folate) or the effect of severity within each subtype.

The major contribution of the present study is the relative risks of mortality for the various kinds of anemia in older, non-disabled, community-dwelling men and women. Although many prior studies have reported on the overall effect of anemia, and some have addressed the effect of

Table 4 RRs from other studies

Reference	First author	Year	*N*	Note on data or subjects	Ages	Average age	Follow-up time	RRs, with explanatory notes as necessary
[21]	Anand	2004	912	Chronic heart failure patients, NYHA Class II–IV	18–55	62	0–26 months	Crude RR = (28% mortality in anemics)/(16% in those not) = 1.8
[17]	da Silveira	2008	310	CAD patients		63	Av 44 months	6.5
[22]	Dunlay	2008	676	Olmstead county (HF patients)		76	Av 5.3 years	Varied by severity of anemia (RRs 1.0–2.4)
[18]	Go	2006	59,772	ANCHOR (HF patients)	20–106	72	<7 years	Varied by hemoglobin level (RRs up to 3.48) and eGFR (up to 5.91)
[20]	Groenveld	2008	153,180	Review article on CHF patients				Crude 1.96. Adjusted 1.46
[23]	Maggioni	2005	7,421	IN-CHF and Val-HeFT (HF patients)	18+	64	1 year	1.96 in IN-CHF; 1.62 in Val-HeFT
[24]	Teng	2009	1,000	HF patients		76	<11 years	1.44
[26]	Ofsthun	2003	44,550	Dialysis patients		60	6 months	2.11
[27]	Robinson	2005	5,517	Dialysis patients	18+	>60	6 months	1.8
[11]	Culleton	2006	17,030	Calgary laboratory patients	66+	75	<3.5 years	Unadjusted 5.01. Adjusted by GFR were 1.53–4.29
[8]	Denny	2006	1,744	EPESE (residents of Durham, NC)	71+	78	8 years	Crude 1.4. Adjusted: Whites 1.8, Blacks 1.7.
[7]	Dong	2008	1,806	Chicago Health Aging Project	65+	80	Av 3.5 years	Whites 1.85, Blacks 1.90
[16]	Isaks	1999	755	Leiden-85 + Study	85+	89	<10 years	In years 0–5 of follow-up, 1.84; in years 5–10, 0.91
[13]	Kikuchi	2001	126	Japanese nursing home residents	70+	83	5 years	Derived from the study: Ages 70–79, 1.8; 80–89, 1.9; 90–99, 1.5.
[14]	Landi	2007	372	Nursing Home Catholic Univ. of Rome	65+	81	2 years	1.56
[12]	Patel	2007	3,075	Health ABC Study	70-79	76	<6 years	Men: White 1.62, Black 0.88; Women: White 2.68, Black 1.17
[9]	Penninx	2006	3,607	EPESE	71+	78	Av 4.1 years	1.63
[10]	Riva	2009	4,501	Residents of Biella, Italy	65–84	73	<4 years	1.86
[15]	Semba	2007	688	Women's Health and Aging Study I	65+	77	<5 years	Type of anemia: 1.99, renal disease; 1.32, unexplained; 0.79, nutritional deficiency vs. non-anemic
[4]	Zakai	2005	5,888	Cardiovascular Health Study (CHS)	65+	73	<12 years	1.38

Recent studies on the effect of anemia on mortality. Study populations with a common comorbid condition [heart failure (HF) or kidney disease (dialysis patients)] appear at the top, and those without at the bottom

severity, only one previous study has reported on the effect of type, and that only amongst older disabled women.

We estimated the effect of anemia type on mortality in both (1) the entire NHANES III database, controlling for other factors, and (2) in a healthy subset. The former might reasonably be considered applicable to the general population of the United States, while the latter a surrogate for the insurance population. If so, the relative risks given in Table 3 can be applied to these populations.

Conflict of interest None.

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