

# Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia

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Clinicians frequently identify anemia in their older patients, but national data on the prevalence and causes of anemia in this population in the United States have been unavailable. Data presented here are from the noninstitutionalized US population assessed in the third National Health and Nutrition Examination Survey (1988-1994). Anemia was defined by World Health Organization criteria; causes of anemia included iron, folate, and B<sub>12</sub> deficiencies, renal insufficiency, anemia of chronic inflammation (ACI), formerly

termed anemia of chronic disease, and unexplained anemia (UA). ACI by definition required normal iron stores with low circulating iron (less than 60  $\mu$ g/dL). After age 50 years, anemia prevalence rates rose rapidly, to a rate greater than 20% at age 85 and older. Overall, 11.0% of men and 10.2% of women 65 years and older were anemic. Of older persons with anemia, evidence of nutrient deficiency was present in one third, ACI or chronic renal disease or both was present in one third, and UA was present in one third. Most

occurrences of anemia were mild; 2.8% of women and 1.6% of men had hemoglobin levels lower than 110 g/L (11 g/dL). Therefore, anemia is common, albeit not severe, in the older population, and a substantial proportion of anemia is of indeterminate cause. The impact of anemia on quality of life, recovery from illness, and functional abilities must be further investigated in older persons. (Blood. 2004;104:2263-2268)

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## Introduction

Anemia is a common condition in the older population, and the prevalence of anemia rises with advancing age. Although it was previously believed that declines in hemoglobin levels might be a normal consequence of aging, evidence has accumulated that anemia does reflect poor health and increased vulnerability to adverse outcomes in older persons. Even in persons 85 years and older, those meeting the World Health Organization (WHO) definition of anemia were found to have higher subsequent mortality rates than persons who were not anemic.<sup>1</sup> In a large retrospective study of persons 65 years and older who were hospitalized for acute myocardial infarction, lower hematocrit levels on admission were associated with higher 30-day mortality rates. Among patients admitted with hematocrit values of 0.33 (33%) or lower, transfusion was associated with a substantial reduction in mortality rate.<sup>2</sup> Older heart failure patients with anemia have also been shown to have higher mortality rates than heart failure patients without anemia.<sup>3</sup> Furthermore, in older women who are not anemic, functional status is better for those with high normal (130-150 g/L [13-15 g/dL]) than with low normal (120-129 g/L [12-12.9 g/dL]) hemoglobin values,<sup>4</sup> calling into question the lower cutoff for defining anemia in older women compared with men.

Multiple studies have estimated prevalence rates of anemia in older persons in the United States, including those performed in clinical populations,<sup>5-7</sup> in local communities,<sup>8-10</sup> and in persons up

to age 75 years.<sup>11,12</sup> However, none of these studies has all the following characteristics: nationally representative sample of community-dwelling persons; no upper age limit, with adequate sample size to make estimates for the oldest-old subset of the population; additional diagnostic tests that make it possible to classify the cause of the anemia. The Third National Health and Nutrition Examination Survey (NHANES III) has all these characteristics and provides the most comprehensive database available for determining age- and sex-specific prevalence rates of anemia in the total US population and for determining causes of anemia in the 65 years and older population.

## Patients, materials, and methods

### Data source

Data for the initial analyses presented here are from phases 1 and 2 of NHANES III (1988-1994). Data used for the estimates related to causes of anemia were limited to phase 2 (1991-1994) of NHANES III because phase 1 did not contain the full complement of laboratory tests necessary for these analyses. Each phase of the study was designed to be a separate national probability sample of the civilian noninstitutionalized population, with no upper age limit. Subjects were sampled using a stratified, multistage probability design that has previously been described in detail.<sup>13</sup> Young children, older persons, African Americans, and Mexican Americans were oversampled, and data are reported for Mexican Americans rather than all

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Hispanics because the number of other Hispanics in the sample was small. Small sample sizes do not permit accurate estimates for other ethnic and racial subgroups.

A full assessment in NHANES III included a home interview and an examination, including phlebotomy for everyone 1 year and older, in a mobile examination center (MEC). Some people were unable to come to the MEC and instead underwent a modified home examination that included phlebotomy. Of the 39 695 persons selected for the study, 86% were interviewed at home, and 79% underwent examination (MEC, 30 818; home, 493). In phases 1 and 2, among persons 65 and older, 5252 were interviewed, 4092 (77.9%) were examined in the MEC, and 403 (7.7%) underwent the modified home examination.

In analyses for phases 1 and 2, hemoglobin levels were determined for 26 372 persons 1 year of age and older, including 4199 people 65 years and older. Blood tests used to characterize causes of anemia were available only in phase 2 for 2096 persons 65 years and older. These analytic samples represent 78%, 80%, and 85% of the total interviewed sample in the respective age groups and phases of the survey.

The protocol and the informed consent form were approved by the appropriate institutional review board.

### Laboratory variables

Detailed documentation of the laboratory methods used in NHANES III has been published<sup>14</sup> and will be briefly summarized. Hemoglobin was determined using a Coulter S-Plus Jr electronic counter (Coulter Electronics, Hialeah, FL). Serum iron and total iron-binding capacity (transferrin) were measured colorimetrically (Alpkem RFA analyzer, Clackamas, OR). Serum ferritin was determined using the Quantimmune Ferritin IRMA kit (Bio-Rad Laboratories, Hercules, CA). Free erythrocyte protoporphyrin was assessed using fluorescence extraction.<sup>15</sup> Folate and vitamin B<sub>12</sub> were measured using the Bio-Rad Laboratories Quantaphase Folate radioassay kit (Bio-Rad). For persons undergoing home examination, it was technically possible to perform only a serum folate determination. Whole blood folate was also measured for persons attending the MEC after a 1:22 dilution, and red blood cell (RBC) folate was calculated according to the equation<sup>14</sup>:  $RBC\ folate = [(whole\ blood\ folate \times 22) - serum\ folate] / (1 - hematocrit/100) / [hematocrit/100]$ .

C-reactive protein (CRP) was determined using latex-enhanced nephelometry (Behring Diagnostics, Somerville, NJ). Serum creatinine was measured by the Jaffe reaction using a Hitachi model 737 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN), and creatinine clearance was computed using the Cockcroft-Gault equation:  $[creatinine\ clearance\ (mL/min) = (140 - age) \times kg\ body\ weight] / [mg/dL\ plasma\ creatinine \times 72]$ . A 15% reduction was given for women.<sup>16</sup>

Plasma glucose levels were determined spectrophotometrically using the Cobas Mira Chemistry System (Roche Diagnostic Systems, Montclair, NJ). Rheumatoid factor was determined according to the Singer-Plotz latex agglutination procedure using the N Latex RF Kit (Behring Diagnostics, Somerville, NJ). Antibody to hepatitis C in serum was measured using direct solid-phase enzyme immunoassay (Abbott Laboratories, North Chicago, IL).

### Definitions of anemia and causes of anemia

In accordance with WHO criteria,<sup>17</sup> anemia in children younger than 5 years was defined as hemoglobin levels lower than 110 g/L (11 g/dL); in girls 6 years and older and in boys 6 to 14 years, it was defined as hemoglobin levels lower than 120 g/L (12 g/dL); and in boys 15 and older, it was defined as hemoglobin levels lower than 130 g/L (13 g/dL). Transferrin saturation was calculated by dividing serum iron by total iron-binding capacity and was considered abnormal if it was less than 15%. Iron deficiency, as previously defined for NHANES III,<sup>18</sup> was considered present if the subject had 2 or 3 of the following criteria: transferrin saturation rate less than 15%, serum ferritin concentration less than 12 ng/mL, and erythrocyte protoporphyrin concentration greater than 1.24 μM. Vitamin B<sub>12</sub> deficiency was defined as serum B<sub>12</sub> concentration less than 147.56 pM (200 pg/mL).<sup>14</sup> Folate deficiency was defined as red blood cell (RBC) folate concentration less than 232.49 nM (102.6 ng/mL). In those who underwent home examination only, folate deficiency was defined as serum folate concentration less than 5.89 nM (2.6 ng/mL).<sup>14</sup>

If they had no evidence of iron, folate, or B<sub>12</sub> deficiency, subjects with anemia were evaluated for other causes of anemia. Subjects were classified as having anemia related to chronic renal disease if the estimated creatinine clearance was less than 30 mL/min. Anemia of chronic inflammation (ACI) was defined as low serum iron count (less than 10.74 μM [ $< 60\ \mu g/dL$ ]) without evidence of iron deficiency. This condition has been traditionally called anemia of chronic disease, but ACI is a more accurate portrayal of the inflammatory condition. It is characterized by reduced levels of circulating serum iron, resulting from reduced intestinal absorption and decreased release of iron by macrophages, despite adequate or increased total iron stores.<sup>19</sup> If subjects with anemia could not be classified into any of these categories, they were considered to have unexplained anemia (UA).

### Demographic variables and comorbidities

Race and ethnicity were self-reported and were classified according to US Bureau of the Census definitions. Subjects were asked if they had ever been told by a doctor that they had asthma, arthritis, stroke, cancer (other than skin cancer), congestive heart failure, or diabetes. Those reporting diabetes were queried as to whether it occurred only during pregnancy and whether they were using insulin. As part of the screening before the examination, subjects were asked if they had had surgery in the past 12 months that might impair their physical functioning. Weight was measured using an electronic digital scale, and height was measured using a stadiometer.<sup>20</sup> Blood pressure was obtained using a mercury manometer after the subject sat quietly for 5 minutes. Three readings were made, with 1-minute intervals between readings, and the second and third blood pressures were averaged.<sup>20</sup> A subject was considered to have hypertension if the average systolic blood pressure was 140 mm Hg or higher, if the diastolic blood pressure was 90 mm Hg or higher, or if a physician said on 2 or more occasions that he or she had high blood pressure.

### Data analysis

Prevalence rates and distributions were estimated for the US population by using appropriate sampling weights that accounted for oversampling and nonresponse to the household interview and physical examination.<sup>21</sup> The reference US population for each phase of the survey was based on the Current Population Survey (CPS) for the mid-point of each phase; the March 1990 CPS was used for phase 1, and the March 1993 CPS was used for phase 2. In comparisons of the small subgroups of subjects classified as having ACI and UA, actual demographic characteristics, hemoglobin levels, and chronic condition prevalence rates associated with these subgroups were used because the sampling weights were not appropriate given their small sizes. Statistical comparisons were performed according to logistic models that adjusted for the characteristics used for sampling (age and race/ethnicity).<sup>22</sup>

## Results

Figure 1 shows the prevalence of anemia for men and women across the full age spectrum. Children 1 to 16 years of age have rates of anemia ranging from 6% to 9%. In the 17- to 49-year-old age group, men have their lowest prevalence of anemia, whereas

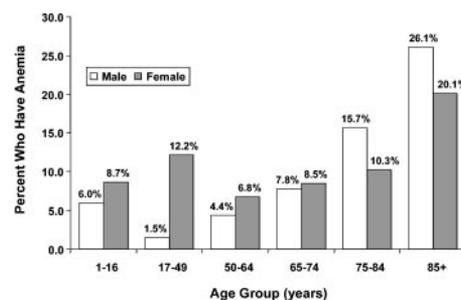


Figure 1. Percentage of persons considered anemic according to age and sex. NHANES III, phases 1 and 2, 1988 to 1994.

**Table 1. Percentages of persons 65 years and older who are anemic, by race/ethnicity and sex: NHANES III, phases 1 and 2, 1988 to 1994**

Race/ethnicity	Men, %	Women, %	Total, %
Non-Hispanic white	9.2	8.7	9.0
Non-Hispanic black	27.5	28.0	27.8
Mexican American	11.5	9.3	10.4
Other	20.4	7.5	14.0
Total	11.0	10.2	10.6

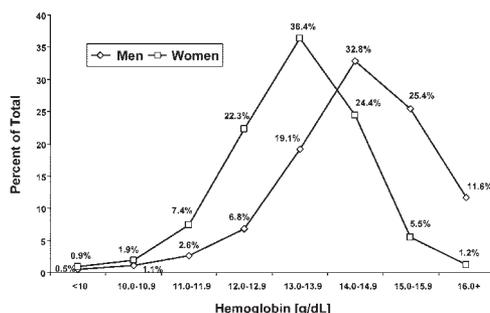
women in their reproductive years have a prevalence greater than 12%. Women’s rates drop by half in the 50- to 64-year-old group and then gradually increase through age 84 years. The prevalence of anemia in women doubles—10% to 20%—from the 75- to 84-year-old to the 85 years and older age group. Men’s prevalence rates of anemia rise more rapidly than women’s from middle age on, nearly doubling in each succeeding age group, as shown in Figure 1. This results in men having a higher prevalence than women after age 75 years and reaching the highest prevalence of 26% at age 85 years and older.

The overall prevalence of anemia in the population 65 years of age and older is 10.6%, with a prevalence of 11.0% for men and 10.2% for women. However, there are substantial differences in prevalence according to race and ethnicity (Table 1). Non-Hispanic whites have the lowest overall prevalence (9.0%), with a slightly higher rate in Mexican Americans (10.4%) but a substantially higher rate in non-Hispanic blacks (27.8%) that is 3 times the prevalence in non-Hispanic whites.

The higher overall prevalence of anemia in older men results from the sex-specific cut-points used to define anemia, with hemoglobin levels of 120 to 130 g/L (12-13 g/dL) defined as anemia in men but normal in women. Figure 2 demonstrates the distribution of hemoglobin for men and women age 65 years and older. The curve for women is shifted markedly to lower values; 32.5% of women have hemoglobin levels lower than 130 g/L (13 g/dL). In this community-dwelling population, less than 1% of persons have hemoglobin values lower than 100 g/L (10 g/dL).

Table 2 shows the distribution of types of anemia in the approximately 3 million older anemic persons in the United States. Overall, deficiencies of iron, folate, or B<sub>12</sub> account for one third of all anemia in the elderly. Within this group, half the anemia is related to iron deficiency. Approximately one third of older anemic persons have ACI (19.7%), anemia of chronic renal failure (8.2%), or both (4.3%), and the remaining one third have UA.

Additional comparisons among older persons with no anemia, those with ACI, and those with UA appear in Table 3. The actual number of persons in the sample with ACI and UA is small, so only the largest differences reach statistical significance. Persons with UA are slightly older than persons without anemia or with ACI, and



**Figure 2. Distribution of hemoglobin in persons 65 years and older according to sex. NHANES III, phases 1 and 2, 1988 to 1994.**

**Table 2. Distribution of types of anemia in persons 65 years and older, United States: NHANES III, phase 2, 1991 to 1994**

Anemia	No. in the United States	Type, %	All anemia, %
<b>With nutrient deficiency</b>			
Iron only	467 000	48.3	16.6
Folate only	181 000	18.8	6.4
B <sub>12</sub> only	166 000	17.2	5.9
Folate and B <sub>12</sub>	56 000	5.8	2.0
Iron with folate or B <sub>12</sub> or both	95 000	9.9	3.4
Total	965 000	100.0	34.3
<b>Without nutrient deficiencies</b>			
Renal insufficiency only	230 000	12.4	8.2
ACI, no renal insufficiency	554 000	30.0	19.7
Renal insufficiency and ACI	120 000	6.5	4.3
UA	945 000	51.1	33.6
Total	1 849 000	100.0	65.7
Total, all anemia	2 814 000	NA	100.0

NA indicates not applicable.

the ACI and UA groups have significantly greater proportions of blacks than does the nonanemic population. The ACI group has a significantly lower proportion of women than does the nonanemic population. Mean hemoglobin levels are similar among subjects with ACI and UA, and both groups have similarly low proportions with severe anemia. Compared with persons with UA, those with ACI have a higher, though not a statistically significant, prevalence of diabetes, congestive heart failure, and stroke. Laboratory testing reveals those with ACI to have an increased prevalence of elevated CRP and positive rheumatoid factor compared with persons with UA, though this difference is only significant for increased CRP. Compared with persons with ACI, persons with UA have higher

**Table 3. Demographic characteristics, hemoglobin level, and prevalence of chronic conditions in total population 65 years and older and in persons 65 years and older with ACI and UA: NHANES III, phase 2, 1991 to 1994**

Characteristic	Total nonanemic population 65 y and older n = 1822	ACI n = 55	UA n = 78
Mean age, y	74.9	75.0†	76.7*
Women, %	56.6	38.2*	47.4
African American, %	15.1	43.6*	30.8*
Mexican American, %	17.5	12.7	7.7
<b>Mean hemoglobin level</b>	14.2	11.8*	11.8*
Less than 110 g/L, %	NA	9.1	11.5
Less than 100 g/L, %	NA	3.6	1.3
<b>Condition, %</b>			
Hypertension	66.8	69.1	68.0
Arthritis	45.4	63.6*	56.4
Diabetes, all	18.8	32.7*	23.1
Insulin-treated diabetes	4.8	12.7	5.1
Congestive heart failure	9.0	12.7	7.7
Asthma	4.3	3.6	3.9
Stroke	9.3	16.4	11.5
Cancer, past 2 y	1.6	1.8	5.1
Cancer more than 2 y ago	6.4	5.5	11.5
Recent surgery, past 12 mo	0.4	1.8	2.6*
Hepatitis C antibody positive	1.3	3.6	3.9
Elevated CRP level, greater than 1.0 mg/dL	11.2	27.3*†	9.0
Rheumatoid factor positive, 30 IU/mL and higher	6.1	20.0*	9.0

NA indicates not applicable.

\*P < .05 versus total 65 years and older population, adjusted for age and race/ethnicity.

†P < .05 versus UA, adjusted for age and race/ethnicity.

rates of reported cancer over the previous 2 years and more than 2 years earlier than that, though this was not statistically significant. As expected, persons with ACI, compared with the nonanemic population, were significantly more likely to have arthritis, diabetes, increased CRP, and positive rheumatoid factor. Persons with UA were significantly more likely to have undergone surgery within the past 12 months.

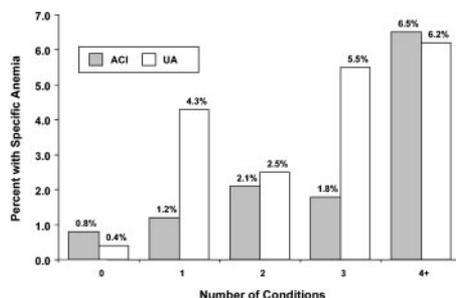
Finally, Figure 3 shows the relationship of comorbidity to ACI and UA. In the total population 65 years and older with none of the conditions considered here, rates of ACI and UA are very low (less than 1%). UA rates increase to between 2.5% and 5.5% in persons with 1, 2, or 3 conditions and are higher than 6% in those with 4 or more conditions. In contrast, the prevalence of ACI remains low in persons with 1, 2, or 3 conditions and only increases substantially when 4 or more conditions are present.

We further analyzed the UA subset to determine the proportion within this category with macrocytosis (mean corpuscular volume [MCV] greater than 100 fL), leucopenia (white blood cell [WBC] count less than  $3 \times 10^9/L$  [ $< 3000/\mu L$ ]), or thrombocytopenia (platelet count less than  $150 \times 10^9/L$  [ $< 150\,000/mm^3$ ]), hematologic features consistent with the diagnosis of myelodysplastic syndrome.<sup>23</sup> Seventeen percent of those with UA, or 5.8% of the total anemic population, met 1 of those 3 criteria.

## Discussion

### Overview of prevalence rates and comparison with other studies

This study revealed that, overall, 11.0% of men and 10.2% of women 65 years and older and living in the community are anemic according to WHO criteria. Had the study also included institutionalized older persons, the overall rates of anemia would likely be even higher. These results are consistent with other community-based studies, including the Established Populations for the Epidemiologic Study of the Elderly (EPESE)<sup>9</sup> and a representative Italian population.<sup>10</sup> There was a pronounced increase in the prevalence of anemia with increasing age within the older population; in the age group 85 years and older, one fifth of women and one fourth of men were anemic, consistent with findings in other studies.<sup>9,10</sup> However, data from the Olmstead County study found a substantially higher prevalence of anemia in men and women 85 years and older (44% and 30%, respectively).<sup>8</sup> That study accrued data through blood tests on residents of the county over a period of several years, and assessments could be made concerning the sickest members of the community, people who would be less likely to participate in a study such as NHANES III.



**Figure 3. Percentage of persons 65 years and older with ACI and UA according to number of conditions present.** NHANES III, phase 2, 1991 to 1994. Conditions include asthma, arthritis, hypertension, stroke, cancer, congestive heart failure, and diabetes.

The high prevalence of anemia in older African Americans has previously been described,<sup>9</sup> as has the lower hemoglobin levels in black people of all ages.<sup>24</sup> Although these differences may be explained by comorbidity, such as chronic kidney disease, known to be increased among black persons, hemoglobin levels are reported to be lower in black persons than in white persons even after taking into account disease status, behavioral risk factors, nutritional intake, and iron status, and it has been debated whether race-specific anemia criteria are indicated.<sup>25-27</sup> In the older population, this can only be justified if the adverse consequences of anemia occur at different levels of hemoglobin in black persons and white persons. More research is required to clarify this.

Men have a higher prevalence of anemia than women simply because the WHO definition is 130 g/L (13 g/dL) in men and 120 g/L (12 g/dL) in women. Figure 2 clearly shows a shift to lower hemoglobin levels in women and reveals that if anemia were defined as hemoglobin levels lower than 130 g/L (13 g/dL) in both men and women, women 65 years and older would have a prevalence of 32.5% compared with 11.0% in men of the same age. It is useful to question whether, 15 years and more after menopause, it is reasonable that women should continue to be considered to have lower hemoglobin levels than men, although higher testosterone levels in men do stimulate higher hemoglobin levels.<sup>28</sup> Ultimately, research on the association between low hemoglobin values and poor health outcomes will help determine whether women with hemoglobin levels between 120 and 130 g/L (12 and 13 g/dL) experience adverse consequences.

### Causes of anemia

Approximately one third of anemia appeared related to a nutrient deficiency, with more than half the subjects in this category deficient in iron, either alone or in combination with folate or B<sub>12</sub> deficiency. Broad definitions of nutrient deficiency were selected to reduce the number of people with actual deficiency who might be misclassified as having no known cause of anemia. Data were not available to document response or lack thereof to treatment with the deficient nutrient. Although the prevalence of anemia from nutrient deficiency may thus be slightly exaggerated, the ease in diagnosis and the safety and low expense of therapy make this an important diagnosis to establish.

Discovering the cause of the nutrient deficiency may also lead to important prevention opportunities beyond correction of the anemia. Most adults with iron deficiency have excess gastrointestinal blood loss, and endoscopic evaluation is likely to find an underlying abnormality. In a study of 100 consecutive older patients with iron-deficiency anemia, Rockey and Cello<sup>29</sup> found 16% with underlying colon cancer or premalignant polyps. Folate deficiency may be a clue for underlying malnutrition or alcohol abuse. Catastrophic neurologic complications from B<sub>12</sub> deficiency may occur despite modest anemia and are readily prevented by timely diagnosis and treatment with supplemental B<sub>12</sub>.<sup>30</sup>

Anemia of chronic disease, the term traditionally used for what we call here ACI, has been defined in a variety of ways, but clinical use of the term has been imprecise, often including any anemia in persons with a high burden of chronic disease without a clearly defined etiology. The new name for this condition reflects current concepts in the pathophysiology of the disease, with elevated inflammatory cytokines stimulating the production of hepcidin, which causes reduced intestinal iron absorption and decreased release of iron by the macrophages.<sup>31,32</sup> One feature of this condition that has remained consistent from its earliest description is reduced levels of circulating serum iron despite adequate or

increased total iron stores,<sup>33</sup> and this was used for the definition we used for ACI.

Distinguishing ACI from iron deficiency can be difficult.<sup>34</sup> A serum ferritin concentration ranging from 20 to 100  $\mu\text{g/dL}$  can be present in iron deficiency and in ACI.<sup>35</sup> Bone marrow assessment of stainable iron or new assays, such as serum transferrin receptor<sup>36</sup> or hepcidin,<sup>37</sup> might improve differentiation of ACI and iron deficiency. With this information unavailable, we have probably underestimated the prevalence of iron deficiency anemia and overestimated the prevalence of ACI. However, it should be noted that this does not influence the proportion of persons we classify as having UA.

We estimate that the remaining one third of older persons with anemia in the United States have UA, though several limitations in the study design might have inflated that estimate. The cross-sectional nature of the study overlooks anemia that may be self-limited, and a more focused history, examination, and laboratory evaluation, including bone marrow examination, would uncover a more specific cause of anemia in a portion of these patients. In a small proportion, early  $B_{12}$  deficiency would be confirmed by elevated methylmalonic acid (MMA) level.<sup>38</sup> Among study subjects with UA, 7.8% had  $B_{12}$  levels ranging from 147.56 to 221.34 pM (200-300 pg/mL), and some would be confirmed to be  $B_{12}$ -deficient by testing MMA. Other uncommon causes of anemia include thalassemia minor, hereditary spherocytosis, autoimmune hemolytic anemia, multiple myeloma, and hypothyroidism.

Myelodysplastic syndrome (MDS) is likely to be a more precise diagnosis for the largest component of subjects now classified as having UA. Although early MDS would be impossible to exclude in an epidemiologic study that cannot obtain bone marrow examination findings for all subjects, more advanced cases are characterized by macrocytosis and are often accompanied by neutropenia or thrombocytopenia. We found that 17.2% of subjects with UA, or 5.8% of the total anemic population, met one or more of these criteria. This is likely an overestimate of how many cases of MDS would be found after a complete assessment because prevalence estimates for this condition show it to be uncommon.<sup>39,40</sup> However, if all anemic persons who met these criteria had the syndrome and several of the rarer causes of anemia listed above were present, then the proportion of anemia related to UA would still be approximately 25%, and it would remain a major category of anemia in the community-dwelling population 65 years of age and older. This high rate of UA was confirmed by a Swedish study that performed full evaluations of anemic subjects, including bone marrow examinations, in 3 representative populations. Those investigators found no cause for anemia in 33% of anemic persons aged 70 years, 23% in persons aged 75 years, and 36% in persons aged 81 years.<sup>41</sup> A recent comprehensive evaluation of causes of anemia in institution-

alized older persons found no cause for the anemia in 45% of nursing home residents.<sup>42</sup>

### Understanding the impact of anemia

In persons of all ages with specific diseases, amelioration of anemia has been shown to have a beneficial impact on morbidity and mortality.<sup>2,43-47</sup> We found that anemia was usually mild in the older population, regardless of its cause. Less severe degrees of anemia (hemoglobin level higher than 100 g/L [ $> 10$  g/dL]) in the elderly have typically not received much clinical attention, though mild anemia may have adverse consequences in old and very old people. Several studies have demonstrated poorer outcomes in older persons with anemia, including mild anemia, than in nonanemic persons of the same age. These studies have shown this effect for mortality,<sup>48</sup> for difficulty in mobility (walking quarter of a mile and climbing stairs) that is prevalent,<sup>4</sup> and for decline over time in objective measures of physical performance.<sup>49</sup> In these observational studies, persons with anemia have more comorbidity, but statistical analysis suggests anemia as an independent predictor. Ultimately, a clinical trial of anemia correction is necessary to prove that mild anemia itself has an independent adverse effect on outcomes relevant to older people, including quality of life, ability to maintain moderate to high levels of physical activity, and maintenance of functional status, particularly related to mobility.

It is important that anemia in older persons receive adequate attention in clinical practice and not be considered simply a normal part of aging. In a population-based study, the diagnosis was listed in the medical records of only one fourth of persons with moderate to severe anemia (hemoglobin level, 110 g/L [11 g/dL] or lower).<sup>8</sup> We demonstrated here that fully one third of anemia in the community-dwelling older population is related to nutrient deficiencies, readily managed with safe and inexpensive therapy and commonly linked to underlying conditions that are important to recognize. Erythropoietin therapy predictably improves anemia in patients with ACI and in those with chronic kidney disease, though treatment guidelines for older patients with those problems must be established. Further research is necessary to better understand the mechanisms and the possible treatment benefits of UA in the large proportion of older anemic patients who have this condition. Future studies of anemia in this population might focus on kinetic causes of anemia, such as the erythropoietin sensing and response mechanisms and the loss of hematopoietic stem cell reserve that may occur with aging.

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