Impact of Anemia and Cardiovascular Disease on Frailty Status of Community-Dwelling Older Women: The Women’s Health and Aging Studies I and II


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Background. The physiological basis of the geriatric syndrome of frailty, a clinical state of increased vulnerability to adverse outcomes such as disability and mortality, remains to be better characterized. We examined the cross-sectional relationship between hemoglobin (Hb) and a recently-validated measure of frailty in community-dwelling older women, and whether this relationship was modified by cardiovascular disease (CVD) status.

Methods. Data were pooled from women 70–80 years old participating in the Women’s Health and Aging Studies I and II (Baltimore, MD, 1992–1996) with known frailty status and Hb ≥ 10 g/dL (n = 670). Logistic regression was used to model the relationship between frailty and Hb, adjusting for demographics, major chronic diseases, and physiologic and functional impairments.

Results. Prevalence of frailty was 14%. Frailty risk was highest at the lowest Hb levels, and lowest at mid-normal Hb levels (e.g., 13–14 g/dL). Mildly low and low-normal Hb concentrations were independently associated with frailty. Compared to an Hb concentration equal to 13.5 g/dL, the adjusted odds of being frail were 1.9 (95% confidence interval: 1.1–3.4) and 1.5 (95% confidence interval: 1.0–2.1) times higher for Hb concentrations equal to 11.5 g/dL and 12 g/dL, respectively. A statistically significant (p < .05) multiplicative interaction between Hb level and CVD status with respect to frailty risk was observed.

Conclusion. In community-dwelling older women, mildly low and low-normal Hb levels were independently associated with increased frailty risk. This risk was synergistically modified by the presence of CVD. These results suggest that mild anemia, and even low-normal Hb levels are independent, potentially modifiable risk factors for frailty in community-dwelling older adults.

Frailty has been increasingly recognized as a major geriatric syndrome (1). During the past few years, several theoretical frameworks for the study of frailty in older adults (2–6) and operational definitions for this syndrome (4,7–8) have been developed. These methodological advances now provide an improved basis for the investigation of the still elusive physiologic basis of frailty. Such knowledge could potentially lead to novel opportunities for improving the health of older adults.

Decreased hemoglobin (Hb) concentration in the whole blood—i.e., anemia—is a common clinical condition in older adults (9) that is often associated with the presence of inflammatory chronic diseases (10). These diseases are known major causes of frailty. Independent associations of anemia with intermediate points of the pathway leading to frailty through age-associated loss of muscle mass—i.e., sarcopenia—have been recently reported (3,11), such as decreased muscle density and area (12), muscle strength (12–13), and physical performance decline (13–15). Additionally, anemia and even low-normal Hb levels have been shown to be independently associated with major outcomes of frailty in community-dwelling older adults, such as mobility difficulty (14), difficulty with basic and instrumental activities of daily living (13), and increased mortality (16). Altogether, these findings suggest a link between anemia and frailty in older adults; however, there are limited empirical data on the direct relationship between Hb and a validated measure of frailty in community-dwelling older populations.

Prevalent cardiovascular disease (CVD) and even subclinical CVD have been identified as major risk factors for frailty in older adults (17), and anemia has been increasingly acknowledged as a major modifiable cause for adverse outcomes in patients with CVD (18). Nonetheless, little is known as to whether the relationship between anemia and frailty is potentially modified by CVD status, or its reciprocal; i.e., whether the association between Hb and frailty risk varies according to CVD status. This information could be particularly relevant for clinical screening.

The objectives of this study were two-fold. First, to determine the role of anemia as an independent risk factor for frailty in community-dwelling older women, we sought to estimate the risk of prevalent frailty as a function of the continuous distribution of Hb, while adjusting for major
demographics and prevalent disease burden that could confound the relationship. Second, to test the a priori hypothesis that the association between Hb and frailty differs according to prevalent CVD status.

**METHODS**

**Study Population**

Data for this cross-sectional analysis came from The Women’s Health and Aging Studies (WHAS) I and II, two prospective population-based studies that recruited complementary groups of community-dwelling women with respect to physical function status. Both studies have been extensively described elsewhere (19,20). Briefly, WHAS I was designed to evaluate the epidemiology of disability progression in 1002 community-dwelling women aged 65 years and older representing the one-third most disabled women living in the community (19). WHAS II was designed to evaluate the epidemiology of disability onset in 436 high-functioning, community-dwelling women aged 70–79 years representing the two-thirds least disabled women living in the community (20). Baseline assessments were performed between November 1992 and February 1995 in WHAS I, and between August 1994 and February 1996 in WHAS II. The Johns Hopkins Medical Institutions Institutional Review Board approved the research protocols. Written informed consent was obtained from all participants.

Baseline data from WHAS I and II were pooled for this analysis. Those participants with missing data on Hb level (n = 180) or with unknown frailty status (n = 3) were excluded. Because this study primarily investigated the effect of Hb levels considered moderately to mildly low or normal on frailty, we excluded those participants with Hb < 10 g/dL (n = 12). The final sample size of this study was 670 participants. Compared with women included in this study, those who were eligible but did not have blood drawn more often reported difficulty with mobility and basic self-care tasks, as well as poorer self-rated health (data not shown). A detailed description of the characteristics of the participants in this analytic sample has been reported elsewhere (14).

**Frailty Status**

The criteria used by Fried and colleagues (2) to define frailty was defined according to the criteria developed by Fried and colleagues (2) (Table 1). On the basis of these standardized criteria, participants were considered frail if they had three or more of the following characteristics: unintentional weight loss, slow walking speed, weakness, self-reported exhaustion, and low physical activity.

**Hb Concentration**

Hb concentration was measured in blood samples collected by venipuncture in sterile vacuum tubes with ethylenediaminetetraacetic acid. Samples were shipped and processed in a commercial laboratory in Teterboro, New Jersey. Hemoglobin was measured by spectrophotometry using the cyanmethemoglobin method.

**CVD**

Prevalent CVD was defined as a definite diagnosis of angina, myocardial infarction, congestive heart failure, and/or a documented history of coronary angioplasty or bypass surgery. These diagnoses were established by physicians who systematically reviewed information on each study participant according to standardized algorithms (21). The following data were reviewed: self-reported medical history collected through standardized face-to-face interviews [including the Rose Questionnaire for Angina (22)], questionnaires filled out by the participant’s primary care physician, list of current medications, and hospital records.

**Other Independent Variables**

Data were available on a number of potential confounders, including: a) demographics (age, race, and education); b) adjudicated disease diagnosis (diabetes mellitus, cancer, rheumatoid arthritis, hip fracture, chronic obstructive or restrictive pulmonary disease, stroke, and lower extremity osteoarthritis, defined as symptomatic or asymptomatic knee or hip osteoarthritis); c) indices of physiologic impairments [creatinine clearance calculated according to the Cockcroft-Gault equation (23), forced expiratory volume in the first second, and level of thyroid-stimulating hormone (<0.4, ≥0.4 to <4.2, and >4.2 mIU/L) (24)]; d) function-related indicators [Mini-Mental State Examination (25), Geriatric Depression Scale–short version (26)]; and e) health habits [smoking status (current, former, or never)]. Variable units are listed in Table 2, unless specified in this section.

**Analysis**

Differences in the distribution of participants’ characteristics by frailty status were assessed using chi-square and

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### Table 1. Frailty Classification Criteria for Women Aged 70–79 Years in the Analytic Sample

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Operational Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weight loss</td>
<td>Unintentional weight loss ≥ 10% since age 60 y, or BMI &lt; 18.5</td>
</tr>
</tbody>
</table>
| • Slowness | Time to walk 4 meters at usual pace, according to height:  
  - <0.65 m/s for height ≤ 1.59 m  
  - <0.76 m/s for height > 1.59 m |
| • Weakness | Grip strength of the dominant hand, according to BMI:  
  - ≤17 kg for BMI ≤ 23  
  - ≤17.3 kg for 23 < BMI ≤ 26  
  - ≤18 kg for 26 < BMI ≤ 29  
  - ≤21 kg for BMI > 29 |
| • Exhaustion | Any of the following during the previous month:  
  - Low usual energy level (<3)  
  - Felt unusually tired in last month  
  - Felt unusually weak in past month |
| • Low physical activity | Self-reported, estimated energy expenditure in kcal based on participation in six activities in the Specific Activity Scale:  
  - ≤90 kcal/wk |

**Decision:** Participants were classified as frail if they met at least three of the five criteria above.

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Note: BMI = body mass index.

*10-point Likert scale 0–10, with 0 being “no energy” and 10 “the most energy that you ever had.”
tests for categorical and continuous variables, respectively. An alpha level of 0.05 was used to determine statistical significance. Scatterplots with lowess smoothing were used for graphical display.

Logistic regression was used to model the relationship between frailty and Hb level, the primary dependent variable of interest, while controlling for confounders. Given the nonlinearity observed in preliminary data exploration, a quadratic curve was fit to model the probability of being frail per the continuous distribution of Hb level. A forward stepwise approach ($p < .05$ for entry, and $p > .05$ for removal) was used to determine a parsimonious multivariate model. Using this strategy, the following were included in the fully adjusted, final model: age, education, prevalent CVD, prevalent rheumatoid arthritis, presence of depressive symptoms, and Mini-Mental State Examination categories. Due to its well established association with anemia, calculated creatinine clearance was forced into the final model, even though it was not statistically significant (likelihood ratio statistic equal to 2.89 following a chi-square distribution with 2 degrees of freedom; $p = .24$). The following variables were not included in the final model because of lack of statistical significance: race, diabetes, cancer, hip fracture, pulmonary disease, lower extremity osteoarthritis, forced expiratory volume in the first second, thyroid stimulating hormone, and smoking status. Difference in frailty risk between Hb concentrations was calculated through the combination of regression coefficients, using procedures that took into account the covariance between coefficients. Conventional mathematical calculations were used to determine the point where the tangent to the frailty–Hb curve had a slope equal to zero. The statistical significance of logistic regression terms

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>All Participants ($N = 670$)</th>
<th>Frail ($N = 94$)</th>
<th>Nonfrail ($N = 576$)</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>74.3 ± 2.9</td>
<td>75.6 ± 3.2</td>
<td>74.1 ± 2.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>493 (77.4)</td>
<td>52 (10.6)</td>
<td>441 (89.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black</td>
<td>144 (22.6)</td>
<td>27 (18.8)</td>
<td>117 (81.3)</td>
<td></td>
</tr>
<tr>
<td>Education (number of years), n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≤8</td>
<td>169 (25.3)</td>
<td>45 (26.6)</td>
<td>124 (73.4)</td>
<td></td>
</tr>
<tr>
<td>9–11</td>
<td>116 (17.3)</td>
<td>19 (16.4)</td>
<td>97 (83.6)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>171 (25.6)</td>
<td>18 (10.5)</td>
<td>153 (89.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;12</td>
<td>213 (31.8)</td>
<td>12 (5.6)</td>
<td>201 (94.4)</td>
<td></td>
</tr>
<tr>
<td>Diseases, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>158 (23.6)</td>
<td>39 (24.7)</td>
<td>119 (75.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>90 (13.4)</td>
<td>20 (22.2)</td>
<td>70 (77.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Cancer</td>
<td>63 (9.4)</td>
<td>14 (22.2)</td>
<td>49 (77.8)</td>
<td>.05</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>15 (2.2)</td>
<td>6 (40.0)</td>
<td>9 (60.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Physiological parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL, mean ± SD</td>
<td>13.2 ± 1.1</td>
<td>12.8 ± 1.3</td>
<td>13.3 ± 1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min/1.73 m², n (%)</td>
<td>198 (33.1)</td>
<td>30 (15.2)</td>
<td>168 (84.6)</td>
<td>.04</td>
</tr>
<tr>
<td>FEV1, L, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Category 1 (≥1.8)</td>
<td>216 (95.4)</td>
<td>10 (4.6)</td>
<td>206 (35.8)</td>
<td></td>
</tr>
<tr>
<td>Category 2 (&gt;1.4 and &lt;1.8)</td>
<td>157 (23.4)</td>
<td>27 (17.2)</td>
<td>130 (82.8)</td>
<td></td>
</tr>
<tr>
<td>Category 3 (&lt;1.4)</td>
<td>181 (27.0)</td>
<td>40 (22.1)</td>
<td>141 (77.9)</td>
<td></td>
</tr>
<tr>
<td>Category 4 (missing)</td>
<td>116 (17.3)</td>
<td>17 (44.7)</td>
<td>99 (55.3)</td>
<td></td>
</tr>
<tr>
<td>Functional indicators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS–short version score ≥ 5, n (%)</td>
<td>105 (15.7)</td>
<td>40 (38.1)</td>
<td>65 (69.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥27</td>
<td>494 (74.7)</td>
<td>52 (10.5)</td>
<td>442 (89.5)</td>
<td></td>
</tr>
<tr>
<td>26–24</td>
<td>119 (18.0)</td>
<td>21 (17.7)</td>
<td>98 (82.4)</td>
<td></td>
</tr>
<tr>
<td>&lt;24</td>
<td>48 (7.3)</td>
<td>20 (41.7)</td>
<td>28 (58.3)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: SD = standard deviation; FEV1 = forced expiratory volume in the first second; GDS = Geriatric Depression Scale (25); MMSE = Mini-Mental State Examination (24).

*Total observations for each variable might not add to 679 due to missing data. Percentages might add to more than 100% due to rounding.

Cardiovascular disease defined as angina, myocardial infarction, congestive heart failure, or documented history of angioplasty or bypass surgery.

Estimated by Cockcroft-Gault equation (23): creatinine clearance (mL/min) = [(140 – age in years) × weight in kg × 0.85]/[72 × serum creatinine in mg/dL]. Creatinine clearance was treated as a continuous covariate.
representing multiplicative interaction between Hb level and CVD status in relation to frailty risk was assessed through the Wald test. Stata 7.0 was used for analysis (Stata Corporation, College Station, TX).

RESULTS

Study Population
The main characteristics of the study population are reported in Table 2. The prevalence of frailty was 14% in this analytic sample. Frailty status was associated in bivariate analysis with increased age, black race, lower education, prevalent CVD and a number of major chronic diseases, lower Hb level, renal and pulmonary impairments, physical disability, depressive symptoms, and lower cognitive function ($p < .05$ for all parameters). Variables not statistically associated with frailty status were prevalent hip fracture ($p = .72$), stroke ($p = .25$), chronic pulmonary disease ($p = .66$), lower-extremity osteoarthritis ($p = .33$), level of thyroid-stimulating hormone ($p = .29$), and smoking status ($p = .24$). Having an Hb level in the bottom quartile ($\leq 12.5 \text{ g/dL}$) was positively associated with all the frailty items listed in Table 1, with the exception of “exhaustion”; specifically, the proportions of participants with Hb $\leq 12.5 \text{ g/dL}$ in those who did and did not manifest each item were the following: shrinking, 39.1% versus 22.5% ($p = .001$); weakness, 33.6% versus 23.3% ($p = .01$); slowness, 37.7% versus 18.8% ($p < .001$); low physical activity, 37.3% versus 21.1% ($p < .001$); and exhaustion, 26.9% versus 25.5% ($p = .77$).

Table 3. Relative Likelihood of Being Frail Associated With Different Hemoglobin Concentrations in the Women’s Health and Aging Studies I and II, Baltimore, Maryland, 1992–1996

<table>
<thead>
<tr>
<th>Hemoglobin Level, g/dL</th>
<th>Fully Adjusted Logistic Regression Model*</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0</td>
<td>7.1</td>
<td>1.8–28.8</td>
<td></td>
</tr>
<tr>
<td>10.5</td>
<td>4.3</td>
<td>1.5–12.5</td>
<td></td>
</tr>
<tr>
<td>11.0</td>
<td>2.8</td>
<td>1.3–6.0</td>
<td></td>
</tr>
<tr>
<td>11.5</td>
<td>1.9</td>
<td>1.1–3.4</td>
<td></td>
</tr>
<tr>
<td>12.0</td>
<td>1.5</td>
<td>1.0–2.1</td>
<td></td>
</tr>
<tr>
<td>12.5</td>
<td>1.2</td>
<td>.95–1.5</td>
<td></td>
</tr>
<tr>
<td>13.0</td>
<td>1.1</td>
<td>.94–1.2</td>
<td></td>
</tr>
<tr>
<td>13.5</td>
<td>1.0</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>14.0</td>
<td>1.0</td>
<td>.90–1.2</td>
<td></td>
</tr>
<tr>
<td>14.5</td>
<td>1.1</td>
<td>.85–1.5</td>
<td></td>
</tr>
<tr>
<td>15.0</td>
<td>1.4</td>
<td>.82–2.3</td>
<td></td>
</tr>
<tr>
<td>15.5</td>
<td>1.8</td>
<td>.82–3.8</td>
<td></td>
</tr>
<tr>
<td>16.0</td>
<td>2.5</td>
<td>.84–7.2</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, education, prevalent cardiovascular disease, prevalent rheumatoid arthritis, calculated creatinine clearance, Geriatric Depression Scale scores, and Mini-Mental Status Examination scores. Units of covariates are as listed in Table 1.

Hb Concentration and Frailty
The relationship between Hb concentration and frailty in the overall study population was curvilinear, with frailty risk being highest around the lowest Hb concentrations and lowest at concentrations in the middle of the World Health Organization (WHO) (27) normal range (i.e., 12–16 g/dL) (Figure 1). The point through which the tangent line to the frailty–Hb curve had a slope equal to zero corresponded to an Hb level of 13.5 g/dL [95% confidence interval (CI): 13.1–13.9], as calculated using the fully adjusted model described previously. Compared to mid-normal Hb levels, concentrations currently classified as mildly low and low-normal were independently associated with an increased risk of being frail (Table 3). For example, the odds of being frail were 1.9 (95% CI: 1.1–3.4) and 1.5 (95% CI: 1.0–2.1) times...
higher for the Hb concentrations of 11.5 g/dL and 12.0 g/dL, respectively, compared to an Hb level of 13.5 g/dL, even after adjustment for major health status indicators and chronic disease burden markers.

Additional, exploratory post hoc analysis was conducted assessing the relationship between frailty status treated as a 3-ordinal measure on the basis of the number of the frailty characteristics listed in Table 1 presented by the participant ("frail" = ≥3; "intermediate" = 1 or 2; and "robust" = 0), and Hb level dichotomized into ≤12.5 g/dL (bottom quartile) versus >12.5 g/dL (top three tertiles). We observed a dose-response pattern, with a stepwise increase in the proportion of participants with Hb ≤12.5 g/dL with frailty severity: 43.6% in the frail group, 26.4% in the intermediate group, and 17.9% in the robust group (nonparametric linear trend test \( p < .001 \)).

**Effect Modification by CVD Status**

The shape of the relationship between frailty and Hb level was significantly modified by CVD status (Figure 2). Among participants without CVD, there was a steep increase in the probability of being frail with declining Hb for concentrations less than 12 g/dL; for Hb between 13 and 15 g/dL, the relationship was flattened; and for Hb concentrations above 15 g/dL, frailty risk increased progressively with higher Hb. The tangent to the frailty–Hb curve had a slope equal to zero at an Hb level of 13.9 g/dL, as calculated using the fully adjusted model described in Table 4. In women with prevalent CVD, a decline in Hb concentration was linearly associated with increased likelihood of being frail throughout the entire range of Hb levels. There was a significant interaction between Hb and CVD with respect to frailty risk (\( p \) values for the multiplicative interaction terms Hb * CVD and Hb2 * CVD were .03 and .03, respectively, in both the age-adjusted and fully adjusted models) (Table 4).

**DISCUSSION**

Little work to date has examined the relationship between Hb level and frailty status defined according to a formal, validated classification criterion in a population-based setting. In this study of community-dwelling older women, we found an independent, nonlinear association between Hb level and frailty, a geriatric syndrome that has been conceptualized as being clinically distinct from aging, disability, or disease (28). Specifically, we found that the risk of being frail...
progressively declined with increasing Hb level up to what is currently considered mid-normal levels, even after adjustment for demographics, presence of major diseases, and disease burden variables. It is interesting that the Hb concentration at which the slope of the relationship between frailty and Hb level was equal to zero was 13.5 g/dL, which is closer to the analogous threshold recently identified for the relationship between Hb level and mortality (14.3 g/dL) (16) than to the WHO anemia diagnostic threshold often used in clinical practice (12 g/dL). We have also found that the presence of CVD modified the relation between Hb level and frailty.

These novel data build on a recent pilot study (29) that showed that frail persons had lower mean Hb levels than did nonfrail persons (29). They are also in agreement with recent findings of analogous curvilinear relationships of Hb level with mobility difficulty (14) and all-cause mortality (16). The finding that a mid-normal Hb level was independently associated with lower risk of frailty compared with mildly low (e.g., 11 g/dL) and low-normal Hb levels (e.g., 12 g/dL) is consistent with recent findings of a dose-response gradient of decreased risk of adverse clinical outcomes with increasing Hb level up to around the WHO mid-normal range (e.g., 13–14 g/dL) (14–15).

The observed relationship between low Hb level and frailty in our data set was not driven by presence of "exhaustion," the item of the frailty phenotype that captures some of the most traditional anemia-related fatigue symptoms. In fact, analysis revealed that an Hb level in the bottom quartile (Hb < 12.5 g/dL) was associated with all items but exhaustion. This latter finding was unexpected and requires further investigation.

Several mechanisms could potentially explain the link between low Hb level and frailty. Low Hb level can diminish the maximal capacity of the cardiopulmonary and musculoskeletal systems to consume oxygen, leading to decreased cardiovascular and muscular conditioning (30). This reduced muscle oxygenation could also contribute to sarcopenia (12). Tissue hypoxia and sarcopenia may cause clinical symptoms such as fatigue and exhaustion, which could subsequently lead to a decrease in the amount and/or intensity of physical activity, and further decline in fitness. The association between anemia and frailty may also indirectly reflect in part the effect of low-grade inflammation, which has long been accepted to play a major role in the development of chronic anemia in older adults, and is also related to frailty through anemia-independent effects on other systems (31–33).

The finding of a synergistic interaction between Hb level and CVD in relation to frailty status is in line with prior work (34) that reported an increased mortality risk associated with low preoperative Hb levels that was more pronounced in patients with CVD than in those without it. The cardiovascular system has a well established, primary role in promoting and modulating the compensatory physiological responses to anemia. When cardiovascular impairments are present, as in persons with CVD, the ability to physiologically compensate for anemia may be limited, which would result in a state of increased clinical vulnerability (captured by the frailty phenotype) that is above and beyond the one that could be expected on the on the basis of the independent adverse impact of CVD and anemia separately. The more gradual decrease in frailty risk with increasing Hb level in those with CVD, as opposed to the sharper risk decrease in those without CVD described in Figure 2, may be understood as a reflection of a state of reduced physiological reserve diminishing the effectiveness of compensatory responses in minimizing one’s clinical vulnerability.

The reason why the frailty–Hb curve in participants with CVD did not turn up at Hb concentrations of ≥15 g/dL, as it did among participants without CVD, remains to be determined. One possible explanation could be survival bias. For example, it is possible that participants with CVD who also had pulmonary disease, an Hb level within the 15–16 g/dL range, and perhaps a high risk for frailty were underrepresented in our study, as a function of greater comorbidity burden preventing participation in study. An additional explanation could be sampling variability, given that there were only 45 participants (6.7%) who had both CVD and pulmonary disease, and, of those, just one had an Hb level > 15 g/dL.

Major strengths of this study included the use of accepted, validated measures of frailty and disease diagnoses, and availability of data on a large number of potential confounders. Nonetheless, several limitations should be acknowledged. First, this was a cross-sectional, nonexperimental study with a relatively small sample size, thus inferences about causality are considerably limited. Second, despite comprehensive adjustment, residual confounding by chronic disease burden should be acknowledged when interpreting these results, and so should the possibility of mild anemia being a marker of underlying subclinical and clinical diseases not considered in this study, such as vitamin B12 deficiency, that could be the real cause of frailty. Randomized clinical trials, in particular, will be critical to circumvent the limitations of observational studies vis-à-vis assessment of the nature of the association between Hb level and frailty. Third, this was a study of community-dwelling older women, thus results should neither be automatically generalized to older men, nor to populations in other clinical settings. Additionally, because this study did not include older men, we could not directly assess the appropriateness of clinically interpreting Hb levels differentially on the basis of sex. Indirectly, though, these data question the rationale for not considering older women with Hb levels within the range of 12–13 g/dL as having “low” Hb, while considering older men with similar Hb levels as anemic. Fourth, for the purpose of simplicity, frailty was treated as a binary outcome. It is possible that the use measures that depict frailty as a continuum might provide additional insight into the relationship between anemia and frailty. Finally, it should be acknowledged that potential effect modification of the relationship between anemia and frailty by type of anemia was not assessed in this study.

Summary

In community-dwelling older women, Hb levels currently perceived as mildly low and even low-normal were independently associated with frailty, and presence of CVD modified the relationship between Hb level and frailty status. Whether the association between anemia and frailty is causal, though, remains to be proven. In this context,
randomized clinical trials will provide unique opportunities to critically assess whether treatment of mild anemia aiming at a target Hb level within the low-normal or possibly mid-normal range (such as 13–14 g/dL) could offer an opportunity for preventing and/or reversing frailty in community-dwelling older adults, analogously to the beneficial health status effects of anemia-related interventions observed in other settings (18,35–37). Finally, further research should evaluate how to best translate the interaction between Hb level and CVD status into frailty-related screening tools and clinical decision-making strategies.

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