Low Hemoglobin Levels and Risk of Developing Depression in the Elderly:
Results From the Prospective PRO.V.A. Study

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ABSTRACT

Objective: Low hemoglobin negatively affects health in the elderly, but research about the association with risk for depression is limited. We investigated the association between baseline hemoglobin concentrations and incident depression in a cohort of nondepressed elderly individuals.

Methods: As part of the Northern Italian Progetto Veneto Anziani (PRO.V.A.) study, randomly drawn, community-dwelling subjects aged ≥ 65 years underwent prospective clinical and laboratory assessments between October 1995 and December 2002. The association between baseline hemoglobin and depression was assessed with adjusted Cox regression analyses. Baseline serum hemoglobin concentrations were further categorized in gender-specific tertiles; anemia was defined as serum hemoglobin < 13 g/dL for men and < 12 g/dL for women. Moreover, hemoglobin concentration was measured at follow-up, and changes in concentration from baseline to follow-up were investigated. Depression was defined by a score of ≥ 11/30 on the validated Geriatric Depression Scale and confirmed by psychogeriatric specialists.

Results: Among 1,303 elderly individuals (566 men, 737 women) without depression at baseline, 294 subjects (177 women, 117 men; global incidence rate = 50 [95% confidence interval (CI), 0–170] per 1,000 patient years) developed depression during 4.4 years of follow-up. Low baseline serum hemoglobin concentration was most strongly associated with incident depression at follow-up in men (hazard ratio [HR] = 1.39; 95% CI, 1.12–1.69; *P* = .002), but not in women (*P* = .50). Men with the lowest baseline tertile hemoglobin concentration (HR = 1.68; 95% CI, = 1.02–3.08; *P* = .04) or with anemia (HR = 2.02; 95% CI, = 1.13–3.64; *P* = .02) had greater risk of depression, whereas findings were nonsignificant for women. Low follow-up hemoglobin concentration in men was less strongly associated with incident depression (HR = 1.15; 95% CI, 1.01–1.33; *P* = .05), as were the lowest endpoint tertile hemoglobin concentration (*P* = .03) and presence of anemia (*P* = .05).

Conclusions: Low baseline hemoglobin strongly predicted incident depression in older men, but not in women.

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Depression is a common condition in the elderly, with a prevalence reaching about 10% among community-dwelling subjects, but with significantly higher prevalences in other settings such as hospitals and nursing homes.[1] Depression is strongly associated with several negative outcomes in the elderly, such as disability, hospitalization, cardiovascular diseases, and mortality.[2,3]

Among less known modifiable risk factors for depression, anemia has raised increasing interest. Anemia is often associated with conditions (eg, cancer, chronic renal failure, malnutrition) that are closely related to an increased risk of depression, probably through decreased quality of life.[4] Moreover, anemia can decrease muscle strength, leading to fatigue, a condition that usually precedes depressed mood.[5,6] Finally, some authors have proposed that anemia also has a pathophysiologic role in depression due to chronic hypo-oxygenation.[7,8] Cross-sectional studies[4,9–11] have shown that anemia is significantly associated with depression. However, the design of these studies did not allow understanding of whether depression precedes anemia or vice versa. Although both depression[12] and anemia[13] are generally more prevalent in women compared to men, possible gender differences in the association between anemia and depression have only insufficiently been investigated, and results have been inconclusive.[9,10] Finally, to the best of our knowledge, the only available longitudinal study[14] showed no significant association between anemia at baseline and the onset of depression during 2 years of follow-up in a cohort of 3,816 elderly people, but data on possible differences between men and women were, unfortunately, not reported.

However, since both anemia[15] and depression[16] are continuously increasing in older people, it is important to determine if anemia is a potential risk factor for depression that can be addressed and whether gender differences exist.

The aim of this work was therefore to investigate the association between baseline serum hemoglobin concentrations and the incidence of depression in a cohort of elderly people without depression at

Clinical Points

- Although several cross-sectional studies pointed toward an association between anemia and depression in the elderly, lack of prospective data have precluded clarification of the directionality of that association.
- Low hemoglobin is associated with risk for depression in elderly men but not women.
- Screening for and treatment of anemia in older men may help decrease depression in the elderly.

baseline during longer-term follow-up, considering also the possible role of gender.

METHODS

Data Source and Subjects

This work is based on data of the Progetto Veneto Anziani (PRO.V.A.) study, an observational cohort study of all community-dwelling subjects aged ≥65 years residing in Camposampiero and Rovigo (two towns in northern Italy surrounded by rural and industrial areas) without using any specific exclusion criteria. The baseline visit was made between October 1995 and November 1997. To avoid a sampling bias, the initial sample was randomly divided into 3 (Camposampiero) and 4 (Rovigo) mutually exclusive subsets that were balanced regarding age and sex distribution. A random sample was selected from the first subset, and the remaining subsets were set aside. In the sampling strategy, age and sex were stratified to keep a male-to-female ratio of 2:3 and to oversample the oldest subjects in order to obtain reliable estimates of conditions with low prevalence rates (such as hip fracture) and to recruit a sizable proportion of disabled subjects. The original aims of this study were to assess the prevalence and the effect of some medical conditions (particularly osteoarticular and cardiovascular diseases) on the social aspect of older persons.[17] The follow-up evaluation was scheduled to occur at 4 years after baseline; the study ended in December 2002.

Figure 1 shows the flowchart of our analysis. Among 3,099 participants enrolled in the study, we excluded 1,219 with prior diagnosis of depression at baseline, 29 without hemoglobin measurement, 133 without follow-up data, and 415 who died during the follow-up period, leaving a final sample of 1,303 participants. By comparison with the sample completing the follow-up, those who dropped out did not differ regarding age ($P=.11$), proportion of men ($P=.84$), Geriatric Depression Scale scores ($P=.41$), or baseline serum hemoglobin levels ($P=.18$).

The local ethical committees of Padova University and the Local Health Units (USSL) n. 15 and n. 18 of the Veneto Region approved the study protocol, and participants gave their written informed consent.

Clinical Data

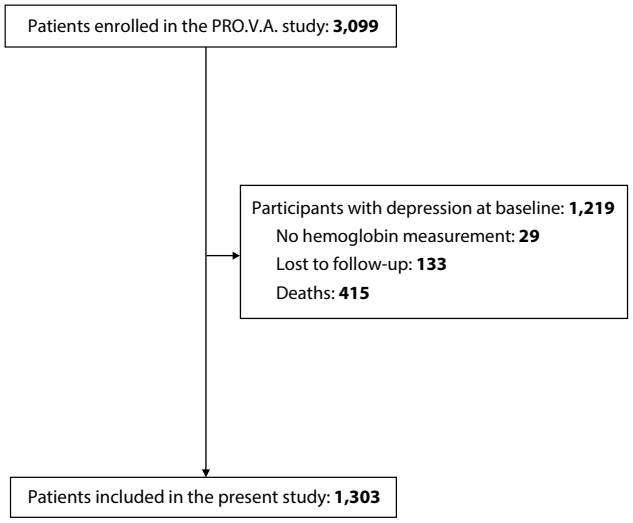
Participants were examined at city hospitals by trained physicians and nurses. Information was collected regarding their physical activity, educational level, smoking, and alcohol drinking during a face-to-face interview. Educational level was classified as ≤5 or >5 years, since 5 years is the cutoff for primary school in Italy. Monthly income was evaluated considering a cutoff value of €500 (US $557) per month. Regular physical activity was defined as ≥4 h/wk (ie, the upper half of the median split of the entire sample) in the previous month of at least moderate physical activity (brisk walking, cycling, gardening, dancing, or physical exercise). Smoking status was classified as "current" versus "previous (for at least 1 year in the past)/never." Alcohol drinking (defined as drinking alcohol in the previous month) and living alone were both categorized as "yes" versus "no." Heavy alcohol drinkers were defined using the criteria suggested by the National Institute of Alcohol Abuse and Alcoholism, ie, more than 15 drinks weekly for men and 8 for women.[18] We collected the following anthropometric parameters: height (measured or estimated from knee-height, when this proxy indicator was more accurate), weight, and body mass index (BMI; in kg/m^2). The Geriatric Nutritional Risk Index (GNRI),[19] an index combining albumin levels and actual weight compared with ideal body weight (Wlo), was assessed to investigate the nutritional status and was calculated as follows:

$$GNRI = [(albumin \times 1.489) + (41.7 \times measured\ weight/Wlo).$$

Several questionnaires were used to evaluate participants' characteristics. Functional status and social independence were assessed using the Index of Independence in Activities of Daily Living (ADL).[20] Cognitive function was assessed using the Mini-Mental State Examination (MMSE).[21]

Participants' clinical status and comorbidities were evaluated by board-certified physicians through standardized questionnaires considering anamnestic data, self-reported symptoms, medical and hospital records, and results from

Figure 1. Flowchart of the PRO.V.A. Study



Abbreviation: PRO.V.A = Progetto Veneto Anziani.

blood tests and physical examination. For the purpose of our study, the following diseases were assessed: hypoacusis, vision impairment, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary diseases, cancer, and hypertension.[17] The diagnosis of vision impairment was made with a visual acuity test, while the diagnosis of hearing impairment was made with audiometry and confirmed by personnel who are experts in ophthalmology or otorhinolaryngology, respectively. Diabetes was defined as fasting plasma glucose levels ≥ 7.0 nmol/L, hemoglobin-A_{1c} (HbA_{1c}) levels ≥ 6.5%, the use of glucose-lowering drugs, or a history of a 2-hour post-load glucose level ≥ 11.1 nmol/L.[22] We considered cardiovascular disease as the presence of one of the following: congestive heart failure; angina requiring a stent, angioplasty, or hospitalization; myocardial infarction; or stroke. Hypertension was defined as the presence of systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medications.[23]

Laboratory Tests

A venous blood sample was obtained after an overnight fast for biochemical tests, which were performed at the central laboratory of Padova hospital (using standard and quality-controlled procedures). As mentioned previously, albumin levels were obtained. Complete blood cell count was measured using a colorimetric enzymatic method with an intra-assay and inter-assay coefficient of variation < 2%, taking hemoglobin as the main parameter of anemia. This parameter was assessed also at follow-up evaluation. Renal function was assessed using the estimated glomerular filtration rate with the Modified Diet in Renal Disease formula.[24] The erythrocyte sedimentation rate was measured using the Westergren method and sodium citrate–anticoagulated blood samples.[25]

Definition of Risk Categories

Since there was a significant difference in baseline serum hemoglobin levels between genders ($P < .0001$), we divided our sample into gender-specific tertiles using the following cutoffs: for men, the ranges were < 13.9 g/dL, 13.9–14.8 g/dL, and ≥ 14.9 g/dL, while for women, the corresponding figures were < 12.8 g/dL, 12.8–13.5 g/dL, and ≥ 13.6 g/dL. At follow-up, the cutoffs for men were 13.6 g/dL and 14.8 g/dL, and the cutoffs for women were 12.8 g/dL and 13.7 g/dL. Anemia was defined using the cutoffs proposed by the World Health Organization (WHO), ie, < 13 g/dL for men and < 12 g/dL for women.[26] A further classification was made according to the mean corpuscular volume (MCV), considering a reference range of 80–100 fL for both genders.[26]

Definition of Outcome

Any presence of depressive symptoms was assessed at baseline and at follow-up with the Geriatric Depression Scale (GDS),[27] a 30-item self-report tool for identifying depression that has been extensively validated for use in the elderly. GDS scores range from 0 to 30, with a score of ≥ 11 being diagnostic for depression. The diagnosis of depression was further confirmed by geriatricians skilled in psychogeriatric medicine using a standardized questionnaire that also checks for additional relevant information, such as signs and symptoms, medical records, and medication use.[28] The geriatricians were blinded to the hemoglobin levels of the participants.

Statistical Analyses

All measures assessed at baseline and at follow-up were used in the data analysis. For continuous variables, normal distributions were tested using the Shapiro-Wilk test. Participants' characteristics were summarized using means (SDs) for continuous variables and counts and percentages for categorical variables between patients with and without a diagnosis of depression at follow-up. Age-adjusted *P* values were calculated for continuous variables comparing the means of the covariates between patients with and without depression at follow-up using a general linear model; for categorical variables, logistic regression was applied.

The rate of incident depression was calculated as the number of new cases of depression per 1,000 persons per year during the follow-up period. Cox proportional hazard models were used to assess the associations between baseline hemoglobin levels and incident depression. The proportional hazards assumption was checked by plotting the Schoenfeld residuals versus time.[29] The covariates included in the final models were those that were statistically significantly different between people with and without depression during follow-up in univariate analyses, first in the total sample for the analyses of the total sample and then separately in men and in women identifying relevant covariates for the sex-stratified analyses. Variables included in the multivariate Cox regression analyses had to be at a *P* value < 0.10 in the respective univariable analyses. Collinearity among covariates was estimated with the variance inflation factor using a value of ≥ 2 as an exclusion criterion. In primary analyses, adjusted Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) were used to compare depression incidence rates, using baseline hemoglobin values as the key independent explanatory variable.

In secondary analyses, we explored the effect of the following hemoglobin-related independent variables on incident depression: (1) baseline hemoglobin values (divided according to gender-specific cutoffs in tertiles), (2) follow-up serum hemoglobin concentrations (as a continuous variable and divided in tertiles), (3) changes in hemoglobin concentrations (as a continuous variable), and (4) anemia at baseline and follow-up (diagnosed according to WHO criteria).

All analyses were performed using SPSS 21.0 for Windows (SPSS Inc, Chicago, Illinois). All statistical tests were 2-tailed, and statistical significance was set at $P \leq .05$. We used Bonferroni correction for the primary outcome, conducting 3 analyses (total sample, men, and women),

Table 1. Baseline and Follow-Up Characteristics of Participants Divided According to the Presence or not of Depression at Follow-Up in the Total Sample, in Men and Women From the PRO.V.A. Study Sample

	Total Sample (n = 1303)			Men (n = 566)			Women (n = 737)		
Patient Characteristics[a]	Depressed (n = 294)	Not Depressed (n = 1009)	*P* Value[b]	Depressed (n = 117)	Not Depressed (n = 449)	*P* Value[b]	Depressed (n = 177)	Not Depressed (n = 560)	*P* Value[b]
Age, mean (SD), y	73.9 (6.9)	74.1 (7.0)	.75[b]	74.4 (7.2)	73.8 (6.9)	.45[b]	73.6 (6.6)	74.2 (7.1)	.29[c]
Women	177 (60.2)	560 (55.5)	.15	…	…	…	…	…	…
General and anthropometric characteristics									
Current smokers	32 (11.0)	101 (10.0)	.85	21 (17.9)	74 (16.5)	.69	11 (6.3)	27 (4.8)	.43
Heavy alcohol drinkers	35 (11.9)	163 (16.2)	.17	33 (28.2)	154 (34.3)	.25	2 (1.1)	9 (1.6)	.64
Educational level (> 5 y)	46 (16.4)	173 (18.1)	.51	24 (20.9)	96 (22.4)	.84	22 (13.3)	77 (14.6)	.61
Monthly income (> €500 [US $557])	105 (36.6)	422 (42.6)	.07	58 (50.4)	238 (53.1)	.68	47 (27.3)	184 (33.9)	.12
Living alone	40 (13.8)	157 (15.7)	.43	12 (10.3)	27 (6.1)	.15	28 (16.2)	130 (23.5)	.05
Physical activity level, ≥ 4 h/wk	63 (21.4)	310 (30.7)	.002	41 (35.0)	181 (40.3)	.33	22 (12.4)	129 (23.0)	.001
ADL score, mean (SD)	5.51 (1.00)	5.47 (1.13)	.60	5.41 (1.13)	5.33 (1.24)	.72	5.41 (1.13)	5.33 (1.24)	.72
GDS score, mean (SD)	6.64 (2.61)	6.14 (2.59)	.004	6.76 (2.40)	6.09 (2.41)	.007	6.55 (2.75)	6.17 (2.72)	.04
MMSE score, mean (SD)	24.90 (4.74)	24.75 (4.91)	.69	25.81 (3.67)	25.46 (4.27)	.20	24.29 (5.25)	24.18 (5.30)	.83
BMI, mean (SD), kg/m^2	27.83 (4.65)	27.98 (4.56)	.61	26.92 (3.61)	27.29 (3.86)	.41	28.44 (5.16)	28.56 (5.00)	.76
GNRI points, mean (SD)	117.46 (9.40)	117.77 (9.42)	.60	116.21 (8.80)	116.53 (8.58)	.83	118.30 (9.72)	118.78 (9.95)	.50
Medical conditions and medications									
Hypoacusis	200 (68.0)	708 (70.3)	.48	96 (82.1)	363 (81.2)	.92	104 (58.8)	345 (61.6)	.75
Vision impairment	129 (43.9)	496 (49.2)	.68	71 (60.7)	298 (66.5)	.35	58 (32.8)	198 (35.4)	.80
Hypertension	214 (72.8)	727 (72.1)	.81	81 (69.2)	317 (70.6)	.76	133 (75.1)	410 (73.3)	.57
CVD	53 (18.0)	151 (15.0)	.18	27 (23.1)	87 (19.4)	.43	26 (14.7)	64 (11.4)	.15
COPD	15 (5.1)	67 (6.6)	.34	8 (6.8)	45 (10.0)	.25	7 (4.0)	22 (3.9)	.98
Diabetes	36 (12.2)	144 (14.3)	.38	16 (13.7)	62 (13.8)	.97	20 (11.3)	82 (14.6)	.27
Cancer	13 (4.4)	60 (5.9)	.32	7 (6.0)	26 (5.8)	.93	6 (3.4)	34 (6.1)	.18
Antipsychotic medications	2 (0.9)	12 (1.5)	.75	2 (2.4)	3 (0.9)	.27	0 (0.0)	9 (2.0)	.12
No. of medications, mean (SD)	2.99 (1.69)	2.83 (1.69)	.20	2.94 (1.68)	2.56 (1.60)	.16	3.01 (1.71)	3.02 (1.73)	.98
Laboratory tests									
ESR, mean (SD), mm/h	17.53 (14.89)	18.89 (15.92)	.23	12.71 (11.12)	13.24 (13.04)	.52	23.30 (16.57)	20.79 (16.20)	.09
eGFR, mean (SD), mL/min	71.94 (18.88)	70.58 (16.72)	.46	77.61 (19.03)	75.48 (16.23)	.15	67.44 (17.70)	66.66 (16.06)	.77

[a]Unless otherwise specified, values are shown as n (%). Apparent discrepancies in percentages for some variables are due to missing data for some subjects.
[b]Unless otherwise specified, *P* values are adjusted for age and gender using a general linear model or logistic regression, as appropriate.
[c]Not adjusted for age.
Abbreviations: ADL = Index of Activities of Daily Living, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, ESR = erythrocyte sedimentation rate, GDS = Geriatric Depression Scale, GNRI = Geriatric Nutrition Risk Index, MMSE = Mini-Mental State Examination.
Symbol: … = not applicable.

with α = .05/3, ie, *P* = .017. Due to the exploratory nature of the secondary analyses, we did not adjust these *P* values for multiple comparisons.

RESULTS

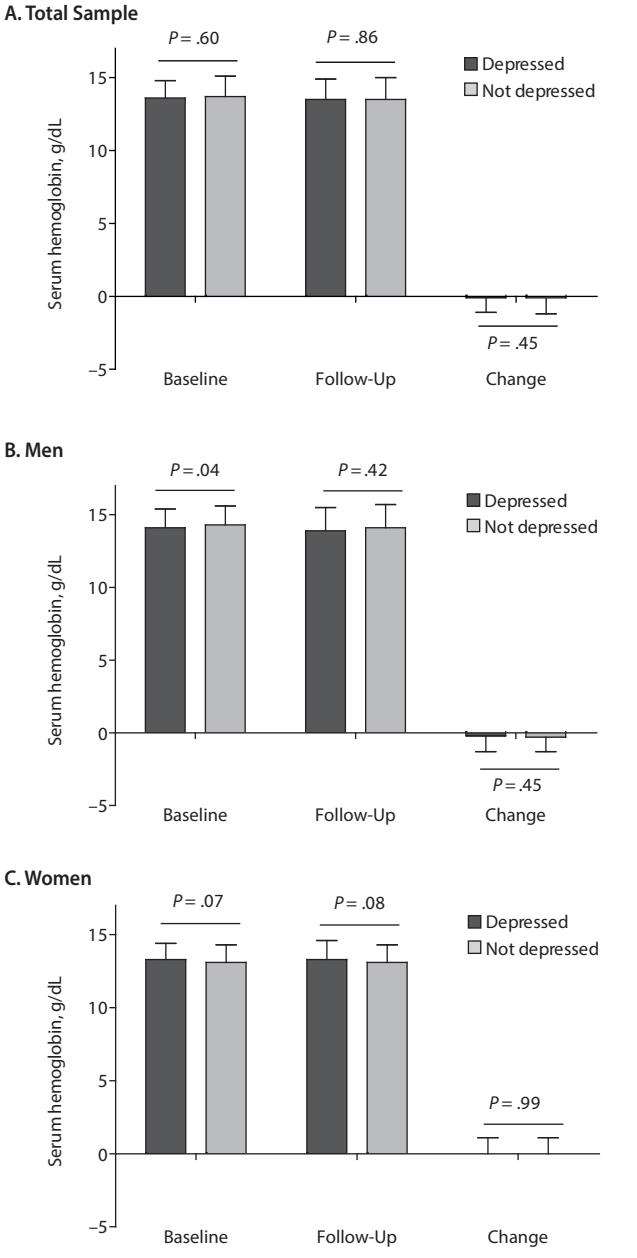
The sample consisted of 1,303 community-dwelling elderly subjects without depression at baseline. The mean (SD) age of the sample was 74.0 (7.0) (range, 65–96) years; 56.6% were female. The mean (SD) baseline serum hemoglobin concentration was significantly higher in men than in women (14.3 [1.3] vs 13.1 [1.1] g/dL; *P* < .0001) without significant differences in the prevalence of anemia (13.8% vs 12.6%; *P* = .51). Sixty-eight participants (5.2% of the whole sample) had a MCV below 80 fL, suggestive of microcytosis, while 51 (3.9%) had a MCV above 100 fL, indicative of macrocytosis.[26]

Table 1 shows the characteristics of the sample according to the diagnosis of depression at follow-up. We identified 294 new cases of depression (men = 117, women = 177) during the 4.4 years of follow-up with a global incidence rate of 50 (95% CI, 0–170) per 1,000 person years. Serum hemoglobin concentrations showed a substantial decline during the follow-up period in the cohort as a whole (*P* < .0001, paired *t* test), although this decrease was statistically significant only in men (*P* < .0001, paired *t* test), but not in women (*P* = .71, paired *t* test).

Compared to nondepressed subjects, depressed men showed significantly lower serum hemoglobin values at baseline (14.1 [1.3] vs 14.4 [1.3] mg/dL; *P* = .04), but no significant differences were apparent for follow-up concentrations (13.9 [1.6] vs 14.1 [1.6] mg/dL; *P* = .42) or for changes between baseline and follow-up (−0.2 [1.1] vs −0.3 [1.0] mg/dL; *P* = .45). Conversely, in women, no differences were evident for hemoglobin concentrations between depressed and nondepressed subjects at baseline (13.3 [1.1] vs 13.1 [1.2] mg/dlL; *P* = .07) or follow-up (13.3 [1.2] vs 13.1 [1.3] mg/dL; *P* = .08) or regarding changes from baseline to follow-up (−0.0 [1.1] vs −0.0 [1.1] mg/dL; *P* = .99) (Figure 2).

Among other investigated characteristics, only lower physical activity (*P* = .002 in the total sample; *P* = .001 in women) and higher GDS scores (*P* = .004 in the total sample; *P* = .007 in men; *P* = .04 in women) were significantly associated with the onset of depression at follow-up (Table 1).

Figure 2. Baseline and Follow-Up Serum Hemoglobin Concentrations and Changes in Concentration From Baseline to Follow-Up in the Presence or Absence of Depression at Follow-Up in (A) the Total Sample, (B) Men, and (C) Women From the PRO.V.A. Study Sample[a]



[a]Unless otherwise specified, data are presented as mean (SD). *P* values are for the comparison between depressed and not depressed individuals, adjusted for age using a general linear model. Changes from baseline to follow-up were also adjusted for baseline hemoglobin concentrations.

Using Cox regression analysis adjusted for potential confounders, baseline hemoglobin concentrations were not significantly associated with the onset of depression during follow-up in the total sample (Table 2). However, in sex-stratified analyses, lower baseline hemoglobin values were associated with a significant increase in future risk for depression in men (HR = 1.39; 95% CI, 1.12–1.69; *P* = .002), but not in women (HR = 0.94; 95% CI, 0.79–1.12;

Table 2. Association Between Baseline, Follow-Up, and Baseline-to–Follow-Up Change in Serum Hemoglobin (Hb) Concentrations and Risk of Depression

	Total Sample				Men				Women			
	Unadjusted Model		Fully Adjusted Model		Unadjusted Model		Fully Adjusted Model		Unadjusted Model		Fully Adjusted Model	
Variable	Hazard Ratio (95% CI)[a]	*P* Value	Hazard Ratio (95% CI)[a,b]	*P* Value	Hazard Ratio (95% CI)[a]	*P* Value	Hazard Ratio (95% CI)[a,b]	*P* Value	Hazard Ratio (95% CI)[a]	*P* Value	Hazard Ratio (95% CI)[a,b]	*P* Value
Baseline Hb	1.03 (0.94–1.11)	.55	1.10 (0.96–1.25)	.15	1.19 (1.04–1.35)	.01	**1.39 (1.12–1.69)**	**.002**	0.85 (0.74–0.98)	.03	0.94 (0.79–1.12)	.50
Baseline Hb tertile[c]												
Tertile 3	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Tertile 2	1.07 (0.80–1.43)	.85	1.16 (0.85–1.58)	.34	1.33 (0.84–2.12)	.23	1.42 (0.86–2.32)	.17	0.93 (0.65–1.35)	.71	1.02 (0.68–1.53)	.92
Tertile 1	1.03 (0.77–1.38)	.85	1.27 (0.88–1.82)	.21	1.47 (0.92–2.34)	.11	**1.68 (1.02–3.08)**	**.04**	0.80 (0.55–1.17)	.25	1.08 (0.68–1.73)	.75
Presence of baseline anemia[d]	1.10 (0.79–1.53)	.59	1.35 (0.92–1.97)	.12	1.68 (1.06–2.66)	.03	**2.02 (1.13–3.64)**	**.02**	0.76 (0.46–1.23)	.26	1.05 (0.62–1.79)	.86
Follow-up Hb	0.96 (0.89–1.04)	.31	0.94 (0.86–1.03)	.21	1.04 (0.96–1.15)	.16	**1.15 (1.01–1.33)**	**.05**	0.83 (0.73–0.97)	.03	0.82 (0.72–1.03)	.09
Follow-up Hb tertile[e]												
Tertile 3	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Tertile 2	0.89 (0.67–1.18)	.42	0.88 (0.66–1.19)	.43	1.11 (0.89–1.23)	.07	1.25 (0.74–1.63)	.45	1.11 (0.70–1.75)	.66	1.12 (0.71–1.79)	.62
Tertile 1	0.82 (0.92–1.09)	.17	0.83 (0.92–1.13)	.24	1.63 (1.43–1.92)	.02	**1.70 (1.02–3.38)**	**.03**	1.08 (0.69–1.67)	.74	1.06 (0.65–1.72)	.81
Presence of follow-up anemia[d]	1.21 (0.88–1.65)	.24	1.14 (0.83–1.58)	.42	1.76 (1.08–2.88)	.02	**1.64 (1.00–2.69)**	**.05**	0.83 (0.55–1.27)	.39	0.85 (0.53–1.35)	.48
Change in Hb (follow-up vs baseline)	1.11 (1.00–1.23)	.04	1.11 (0.99–1.24)	.07	1.17 (0.99–1.39)	.07	1.18 (0.98–1.39)	.09	1.07 (0.94–1.23)	.31	1.15 (0.97–1.37)	.11

[a]Unless otherwise specified, data are presented as hazard ratios (95% CI). Significant results ($P < .05$) are shown in boldface.
[b]Fully adjusted models included the following covariates: baseline age (as continuous), gender (only in the analyses of the total sample), living alone (all yes vs no), monthly income (≤€500 [US $557] vs >€500 [US $557]), baseline scores on the Geriatric Depression Scale, serum erythrocyte sedimentation rate, and serum hemoglobin concentrations at follow-up (for baseline hemoglobin parameters) or baseline hemoglobin values (for changes in hemoglobin) (both as continuous).
[c]Baseline: Tertile 1: serum Hb < 13.9 g/dL (men), < 12.8 g/dL (women). Tertile 2: serum Hb 13.9–14.8 g/dL (men), 12.8–13.5 g/dL (women). Tertile 3 (reference group): serum Hb ≥ 14.9 g/dL (men), ≥ 13.6 g/dL (women).
[d]Anemia was defined using the criteria proposed by World Health Organization[26] (< 13 g/dL in men and < 12 g/dL in women).
[e]Follow-up: Tertile 1: serum Hb < 13.6 g/dL (men), < 12.8 g/dL (women). Tertile 2: serum Hb 13.6–14.8 g/dL (men), 12.8–13.7 g/dL (women). Tertile 3 (reference group): serum Hb > 14.8 g/dL (men), > 13.7 g/dL (women).

$P = .50$). Secondary analyses confirmed these findings since men in the lowest baseline hemoglobin tertile carried a significantly higher risk for developing depression during follow-up (HR = 1.68; 95% CI, 1.02–3.08; $P = .04$), while women did not show a significant correlation between the lowest baseline hemoglobin tertile and depression at follow-up (HR = 1.08; 95% CI, 0.68–1.73; $P = .75$). Using the diagnosis of anemia at baseline instead of tertiles, we observed a significantly higher risk of depression in anemic men (HR = 2.02; 95% CI, 1.13–3.64; $P = .02$), but not in women (HR = 1.05; 95% CI, 0.62–1.79; $P = .86$) (Table 2).

These findings were substantially corroborated in analyses of follow-up hemoglobin values, including mean hemoglobin concentrations, the lowest hemoglobin tertile, and anemia (Table 2). Lower follow-up hemoglobin concentration was again associated with a significant increase in the presence of depression only in men (HR = 1.15; 95% CI, 1.01–1.33; $P = .05$), and the same was true only in men in the lowest hemoglobin tertile (HR = 1.70; 95% CI, 1.02–3.38; $P = .03$) or with anemia at follow-up (HR = 1.64; 95% CI, 1.00–2.69; $P = .05$). Conversely, changes in hemoglobin between baseline and follow-up were not associated with the onset of depression at follow-up in the total sample or after stratifying for gender (Table 2).

DISCUSSION

In the present study, we found a significant association between baseline hemoglobin concentrations and the development of depression during 4.4 years of follow-up in older men, but not women, without depression at baseline. This sex-specific finding of a significantly increased risk for depression in men with low hemoglobin but not in women was further corroborated using follow-up hemoglobin values, albeit with a somewhat weaker association than for baseline hemoglobin values.

Although neither hemoglobin tertile nor anemia status was associated with higher baseline depression scores in either men or women, during the follow-up period, men in the lowest hemoglobin tertile and those with anemia had a higher risk of developing depression than the other groups, while in women this finding was not evident, suggesting important gender differences. Several reasons could help explain these findings. First, there may be a difference in potential risk and protective factors for depression between genders (eg, anxiety disorders, trauma, alcohol use/abuse).[30,31] However, the role of all these factors seems to be marginal in our study, since we adjusted for all these potentially confounding variables and only physical activity level and baseline GDS scores were significant predictors of incident depression. Second, it is possible that, since women had a longer period during their life than men with lower hemoglobin values,[32] they might develop offsetting pathways that guarantee sufficient peripheral oxygenation with fewer consequences for brain function. Exposure to chronic hypoxia has been shown to stimulate compensatory pathways in mammals (including humans), which are characterized by an initial increase in cerebral blood flow, a further increase in hemoglobin (due to the action of erythropoietin), and, if persistent, a structural modification of the brain consisting of increased brain capillary density.[33] One could speculate that, in anemic people, the second pathway is somewhat deficient, leading to an increased risk of depression or other neurologic conditions, but further research is needed to substantiate or refute this hypothesis.

Our findings partially contrast with those present in literature from cross-sectional studies. Umegaki et al[10] reported that low hemoglobin status was associated with depression in older women and not in men. A possible explanation of these differences could be related to the different settings between our and that previous study[10] (community-dwelling vs older people at high risk of requiring care), different races (Asian vs white), the method for assessing depression (simple question of if they felt depressed vs GDS and confirmation by an expert), and the covariates for which the elaborations were adjusted.

Finally, to the best of our knowledge, only 1 prospective study[14] on this topic was published reporting that anemia was not associated with the onset of depression in a large cohort of community-dwelling older people. Unfortunately, those authors did not investigate the potential gender-specific role in the mediating effect of low hemoglobin that seems to be relevant in our prospectively assessed sample. Therefore, further research is needed to investigate both the role of hemoglobin and any gender specificity, as the identification and treatment of low hemoglobin and anemia would be a relatively simple preventive intervention to reduce the incidence of old-age depression, which is associated with a significant morbidity burden and mortality risk.[2,3]

The current study has some limitations that should be taken into consideration. First, we did not have sufficient information on the different possible etiologies of low hemoglobin levels. We did not have data to consider specific medical causes of anemia in the elderly, including liver diseases, gastrointestinal occult blood loss, and thalassemia, the latter of which is a common condition at the latitude where PRO.V.A. study was conducted.[34] Moreover, some vitamin deficiencies (like vitamin B_{12} or folate) could play an important role, as they are common causes of anemia in the elderly, but also have independent neurotrophic functions.[35] However, only a small percentage of our study population (3.9%) had values of MCV suggestive of clinical deficiency of folate and/or vitamin B_{12} at baseline. Second, we lacked information about possible interventions to address anemia during the follow-up period, which may have influenced the results. It was shown in selected contexts (eg, hip fracture, cancer) that the relief from anemia is followed by an improvement in depressed mood.[36,37] Thus, since, in the present study, none of the patients received treatment of anemia to examine if the depression could be decreased that way, it remains unclear if anemia is associated with true depression or if depression-like symptoms are a result

of fatigue and other anemia-related symptoms. Future studies are needed to further disentangle this relationship. Third, although we used a reliable method for diagnosing depression, we did not use the gold standard method of a structured clinical interview combined with a clinical interview by an experienced mental health professional. The lack of a research interview may also partly be related to the relatively high rate of depression in our sample of elderly Italian residents aged ≥65 years. While the prevalence of a formal diagnosis of depression may in some surveys be as low as 5%–10% in those older than 75 years, the prevalence of reports by the elderly of relevant depressive symptoms is significantly higher, reaching up to 37.5%.[2] Moreover, in a recent survey, older Italian people had the highest prevalence of depression among 6 European countries.[38] Finally, the PRO.V.A. study was conducted about 20 years ago, and the possibility of outdated results should be considered, particularly as new diagnostic tools for the identification of anemia and new therapies for depression have emerged. Nevertheless, the biological constructs of anemia and depression have not changed substantially, strengthening the relevance of the findings for current practice.

In conclusion, low serum hemoglobin concentrations and anemia at baseline were associated with a greater risk of depression over a 4.4-year follow-up in elderly men, but not in women. Since low hemoglobin levels are very common in the elderly, clinicians should screen for low hemoglobin levels and seek to identify biological causes. Further research is needed to confirm our findings, particularly about gender differences, and to assess if prevention or correction of anemia is able to decrease the risk for or delay the progression to depression in the vulnerable population of the elderly.

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