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Anemia Is Associated With Depression in Older Adults: Results From the InCHIANTI Study

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Background. Depression is a common disorder among older adults, and it has been associated with adverse outcomes, including increased risk of morbidity and mortality as well as incomplete or delayed recovery from illness and disability. The objective of this study was to examine whether depressive symptoms and anemia are associated among older adults living in the community.

Methods. We used data from the ''Invecchiare in Chianti'' (Aging in the Chianti area, InCHIANTI) study, a prospective population-based study of older people living in the community. Anemia was defined by the World Health Organization (WHO) criteria: hemoglobin concentration below 12 g/dl in women and below 13 g/dl in men. Depressive symptoms were measured by using the Center for Epidemiological Studies Depression Scale (CES-D). Participants with a CES-D score $\geq$16 were considered to be depressed.

Results. Mean age of the 986 participants was 75 years, and 56% were female; 313 (32%) study participants were depressed. Anemia was recorded in 48 of the 313 (15%) participants with depression and in 53 of the 673 (8%) participants without depression ($p < .001$). After adjusting for potential confounders, depression was associated with a significant higher risk of anemia (odds ratio = 1.93; 95% confidence interval, 1.19–3.13). The risk of anemia progressively and significantly increased with increasing CES-D score (signifying more severe depression). Compared with nondepressed participants (CES-D score <16), the odds ratio for anemia were 1.74, 2.04, and 2.10 for participants with mild (score = 16–20), moderate (score = 21–26), and severe depression (score > 26), respectively (p for linear trend = .01).

Conclusions. Depressive symptoms are associated with anemia in a general population of older persons living in the community.

DEPRESSION in the older population is a major health issue, both because of its high prevalence and because of its adverse heath consequences. About 12%–20% of community-dwelling older person suffer from symptoms of depression (1,2). Many cross-sectional studies have demonstrated that, compared with nondepressed persons, depressed older persons have poorer health status, higher prevalence of disability, and more severe comorbidity (3,4). In addition, longitudinal studies have shown that depression represents a risk factor for adverse outcomes including increased morbidity, mortality, and incomplete or delayed recovery from illness and disability (5–8).

Anemia is rather common in old age with a prevalence of about 13% in persons aged 70 years or older (9). This condition is assumed to be due to underlying disease such as cancer, renal failure, and infectious disease, and it has been associated with a number of other comorbidities, such as cardiovascular disease (10). This high burden of comorbidity may negatively affect quality of life and lead to the onset of depressive symptoms (11). Moreover, in studies conducted in hemodialysis patients (12,13), it has been shown that anemia directly affects brain function, and it is responsible for the cognitive impairments and symptoms frequently suffered by persons with chronic renal failure (confusion, inability to concentrate, decreased mental alertness, and impaired memory). Reduced muscle strength and fatigue are commonly associated with anemia and may have detrimental effects on participants' quality of life, therefore facilitating the development of depressive symptoms (14,15). Finally, malnutrition, a common feature in depressed individuals, may be responsible for anemia (10,16). Despite numerous hypothetical pathways suggesting a link between anemia and depression, the association between these two common conditions has rarely been explored in a general population of older adults (17). Therefore, the aim of the present study is to examine whether depressive symptoms are associated with anemia, independent of comorbidity and other potential confounders.

Methods

We used data from the ''Invecchiare in Chianti'' (Aging in the Chianti area, InCHIANTI) study, a population-based study of older people conducted by the Italian National Research Council of Aging (INRCA, Florence, Italy). The InCHIANTI study includes 1156 participants aged 65 years and older who were randomly selected from the residents in two towns of the Chianti geographic area (Greve In Chianti and Bagno a Ripoli, Tuscany, Italy) (18).

Anemia

Details on blood sampling and determination of biological parameters are reported elsewhere (14,15,18). Anemia was defined by the World Health Organization (WHO) criteria (19): Hemoglobin concentration below 12 g/dl in women and below 13 g/dl in men. A ratio between serum transferrin receptor and log(ferritin) above 1.5 was used to define iron deficiency (20). A cutoff of 350 pg/ml (258 pmol/L) was used to identify vitamin B12 deficiency (21).

Depression

Depressive symptoms were measured by using the 20-item Center for Epidemiological Studies Depression Scale (CES-D) (22). Participants with a CES-D score $\geq$16 were considered to be depressed (23,24). In addition, to explore a potential trend between depressive symptom severity and anemia, we defined four participant groups by CES-D score, based on cutoffs previously reported (25): (1) few or no symptoms of depression (CES-D score $<$ 16) ($n = 673$), (2) mild depressive symptoms (score = 16–20) ($n = 126$), (3) moderate depressive symptoms (score = 21–26) ($n = 96$), and (4) severe depression (score $>$ 26) ($n = 91$).

Covariates

A Mini-Mental State Examination (MMSE) score below 18 was used to define cognitive impairment (26,27). The presence of comorbid conditions was determined using an adjudication process that included self-reported history, medical examination data, and medical records information (18). Kidney disease was determined by a serum creatinine level above 1.5 mg/dl in women and above 1.7 mg/dl in men. Based on tertiles of interleukin-6, participants were classified in three groups. Assessment of daily caloric and protein intake was performed based on the questionnaire of the European Prospective Investigation into Cancer and Nutrition (28). Drugs were coded according to the Anatomical Therapeutic and Chemical codes (29).

Study Sample and Statistical Analyses

From the initial sample of 1156 participants, we excluded persons with missing data on hemoglobin level ($n = 119$, 10.3%) or CES-D score ($n = 76$, 6.6%). This selection resulted in a final sample size of 986 participants. In comparison to those who were excluded from study participation due to incomplete data ($n = 170$), those included in the study were significantly younger (75 $\pm$ 7 vs 82 $\pm$ 9 years, $p < .001$) and tended to be less often female (56% vs 62%, $p = .18$).

Differences between depressed and nondepressed participants in categorical parameters were tested using the chi-square test. Differences between continuous variables were assessed by analysis of variance comparisons for normally distributed parameters; alternatively, the Kruskal–Wallis test was adopted. To establish whether depression represented a risk factor for anemia, a logistic regression model was performed in the 986 participants included in this study. To explore a potential trend between depressive symptom severity and anemia, an additional logistic regression model was conducted, using categorization of the CES-D scores as described above. Variables considered for adjustment were those associated with depression at $p \leq .10$ in the univariate analyses. All analyses were performed using SPSS for Windows version 10.0 (Chicago, IL).

Results

Participant Characteristics

Mean ($\pm$ standard deviation) age of the 986 participants entering this study was 75 ($\pm$7) years, and 56% of the study population was female. The mean ($\pm$ standard deviation) CES-D score in the total sample was 12.8 ($\pm$8.7) (range 0–48), and 313 (32%) of the study participants were depressed (CES-D score $\geq$ 16). Other characteristics of the study population are summarized in Table 1. Compared with nondepressed participants, those with depression were older, more likely to be female and enrolled in the Bagno a Ripoli site, less likely to be smokers and drinkers, had a lower education, had a higher prevalence of cognitive impairment, and presented a higher number of diseases. In particular, depression was associated with a higher prevalence of coronary artery disease, peripheral artery disease, congestive heart failure, and history of cancer. Finally, participants with depression were more likely using antidepressant medication, nonsteroidal anti-inflammatory dugs, and acetylsalicylic acid.

Depression and Anemia

Anemia was identified in 101 (10%) study participants: 43 (10%) men and 58 (10%) women. As shown in Table 2, anemia was present in 48/313 (15%) participants with depression and in 53/673 (8%) participants without depression ($p < .001$). After adjusting for potential confounders, depression was associated with a significantly increased risk of anemia (odds ratio [OR] = 1.93; 95% confidence interval [CI], 1.19–3.13). In the fully adjusted model, no significant interaction was observed between depression and sex ($p = .30$) and between depression and age ($p = .35$) on the risk of anemia.

The association between depression and anemia was persistent using a CES-D cutoff of 21 to define depression. Compared with participants scoring $<$ 21, those with a score of 21 or higher were more likely to present with anemia (anemia among depressed participants: 30/187 [16%] vs anemia among nondepressed participants: 71/799 [9%]; $p = .004$), and this association was confirmed after adjusting for potential confounders (OR = 1.78; 95% CI, 1.06–3.00).

As shown in Table 2, depression was still significantly associated with anemia after exclusion of anemia related to iron (transferrin receptor/log[ferritin] $<$ 1.5) (OR = 2.11; 95% CI, 1.23–3.60) or vitamin B12 deficiency (OR = 1.96; 95% CI, 1.01–3.80). To explore whether poor health status or cognitive impairment could explain the association between depression and anemia, we repeated analyses after excluding participants with relevant comorbidities (such as congestive heart failure, kidney disease, history of cancer, or cognitive impairment). These analysis also yielded significant associations of depression with anemia.

Figure 1 summarizes the ORs for anemia across different groups, according to CES-D scores. After adjusting for

Table 1. Baseline Characteristics According to Depression Status

Characteristic	No Depression $N = 673$ (%)	Depression $N = 313$ (%)	p*
Age			<.001
<80 y	559 (83)	211 (67)	
≥80 y	114 (17)	102 (33)	
Female sex	322 (48)	232 (74)	<.001
Site			.06
Bagno a Ripoli	342 (51)	179 (56)	
Greve in Chianti	331 (49)	134 (43)	
Education			.06
0–5 y	480 (71)	244 (78)	
6–8 y	122 (18)	36 (12)	
9–13 y	47 (7)	20 (6)	
>13 y	23 (3)	13 (4)	
Body mass index			.23
<25 kg/m^2	171 (25)	95 (30)	
25–29.9 kg/m^2	340 (51)	173 (46)	
≥30 kg/m^2	162 (24)	75 (24)	
Smoking			<.001
Never	349 (52)	227 (73)	
Former	241 (36)	56 (18)	
Current	83 (12)	30 (10)	
Alcohol use	443 (66)	171 (55)	.001
Cognitive impairment†	15 (2)	14 (5)	.05
No. of diseases, mean ± *SD*	2.6 ± 1.1	2.7 ± 1.2	.09
Diabetes	71 (10)	31 (10)	.76
Coronary artery disease	56 (8)	37 (12)	.08
Peripheral artery disease	48 (7)	32 (10)	.09
Congestive heart failure	24 (4)	22 (7)	.02
Stroke	38 (6)	23 (7)	.30
Pulmonary disease	45 (7)	20 (6)	.86
History of cancer	36 (5)	26 (8)	.08
Gastric disease	33 (5)	16 (5)	.89
Peptic ulcer	104 (16)	45 (14)	.66
Renal failure‡	6 (1)	5 (2)	.33
Albumin (g/dL), mean ± *SD*	4.2 ± 0.3	4.2 ± 0.3	.13
Energy intake (kcal/kg per day)	28.8 ± 8.4	28.0 ± 8.1	.15
Protein intake (g/kg per day)	1.1 ± 0.3	1.1 ± 0.3	.32
IL-6 (pg/mL) tertiles			.65
<1.03	217 (32)	110 (35)	
1.03–1.84	227 (34)	100 (32)	
≥1.85	228 (34)	101 (33)	
Use of antidepressants	13 (2)	24 (8)	<.001
Use of NSAIDs	122 (18)	90 (29)	<.001
Use of ASA	92 (14)	56 (18)	.08

Notes: Depression was defined as Center for Epidemiological Studies Depression Scale (CES-D) score ≥ 16.

*p values are based on chi-square test for categorical variables, analysis of variance for continuous variables.

†Cognitive impairment was defined by Mini-Mental State Examination score < 18.

‡Renal failure was determined by a serum creatinine level above 1.5 mg/dL in women and above 1.7 mg/dL in men.

SD = standard deviation; NSAIDs = nonsteroidal anti-inflammatory drugs; ASA = acetylsalicylic acid.

potential confounders, the risk of anemia progressively and significantly increased as CES-D score increments increased (signifying more severe depression) (p for linear trend = .01). Compared with nondepressed participants whose CES-D score was <16, the ORs for anemia were 1.74, 2.04, and 2.10 for participants with mild (score = 16–20), moderate (score = 21–26), and severe depression (score > 26), respectively.

Table 2. Association Between Depression and Anemia

Patients With	N	Anemia	p	OR (95% CI) for Anemia*
Total sample				
No depression	673	53 (8%)	<.001	1
Depression	313	48 (15%)		1.93 (1.19–3.13)
Sample without congestive heart failure, kidney disease, and history of cancer				
No depression	586	45 (8%)	.001	1
Depression	255	39 (15%)		2.06 (1.21–3.49)
Sample without cognitive impairment†				
No depression	658	49 (7%)	.001	1
Depression	299	43 (14%)		1.93 (1.17–3.19)
Sample without iron deficiency anemia‡				
No depression	657	37 (6%)	<.001	1
Depression	305	40 (13%)		2.11 (1.23–3.60)
Sample without vitamin B12 deficiency anemia¶				
No depression	644	24 (4%)	.003	1
Depression	289	24 (8%)		1.96 (1.01–3.80)

Notes: *Adjusted for age, sex, site, education, smoking, alcohol use, cognitive impairment, number of diseases, coronary artery disease, peripheral artery disease, congestive heart failure, history of cancer, use of antidepressants, use of nonsteroidal anti-inflammatory drugs, and use of acetylsalicylic acid.

†Cognitive impairment was defined by Mini-Mental State Examination score < 18.

‡Iron deficiency was defined by (serum transferrin receptor/log[ferritin] < 1.5).

¶Vitamin B12 deficiency was defined by vitamin B12 < 350 pg/ml (258 pmol/L).

OR = odds ratio; CI = confidence interval; CES-D = Center for Epidemiological Studies Depression Scale. Depression was defined as CES-D ≥ 16; anemia was defined as Hb < 12 g/dL for women and < 13 g/dL for men.

Discussion

Based on our findings among persons living in the community, depression appears to be associated with anemia, irrespective of comorbidity and other potential confounders. This association increases with severity of depressive symptoms.

How could we explain a link between depression and anemia? It has been hypothesized that psychological distress can activate neuroregulated biological processes. This activation can result in a diminished ability to combat pathological processes, thus favoring the onset of negative outcomes such as anemia. This phenomenon, described by Engel (30) as the ''giving-up–given-up complex,'' could explain the increased risk of adverse outcomes observed among depressed participants. According to this hypothesis, depression adversely affects cardiac, gastrointestinal, endocrine, neurologic, and immune processes by increasing sympathetic tone and decreasing vagal tone (31). More specifically, the higher risk of anemia that we observed among depressed participants may be due to a number of factors. First, psychological distress has been associated with an increased risk of occult bleeding, which can be responsible for a higher prevalence of anemia among depressed persons (32). Second, the increased sympathetic

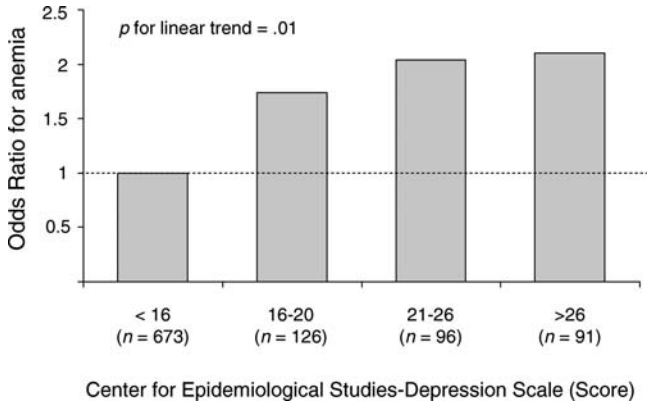

Figure 1. Odds ratio for anemia according to Center for Epidemiological Studies-Depression Scale (CES-D) score (CES-D <16 is the reference group). Analysis is adjusted for age, sex, site, education, smoking, alcohol use, cognitive impairment, number of diseases, coronary artery disease, peripheral artery disease, congestive heart failure, history of cancer, use of antidepressants, use of nonsteroidal anti-inflammatory dugs, and use of acetylsalicylic acid.

tone, observed among depressed persons (31), can regulate bone marrow microenvironment, affecting erythropoiesis (33). Third, anemia can represent a consequence of malnutrition among depressed persons (16). However, the fact that daily caloric and protein intake did not differ significantly according to depressive status makes this explanation unlikely.

Another possible explanation for our findings is that depressive symptoms may occur as a consequence of anemia. Anemia may directly affect brain function. Some studies conducted in hemodialysis patients (12,13) have shown that anemia appears to contribute to impaired cognitive function and that persons with chronic renal failure frequently suffer from confusion, inability to concentrate, decreased mental alertness, and impaired memory. In addition, acute isovolemic anemia results in subtle slowing of data-processing ability in humans and degrades memory (12). Previous studies conducted among hemodialysis patients (13,34) have shown that correction of renal anemia with erythropoietin improves quality of life, cognition, and depressive symptoms. This improvement of psychological symptoms seems to be mediated by an increment of oxygen delivery to the brain and particularly to frontotemporal and subcortical brain structures, which are involved in the depression pathway (35,36). Finally, fatigue, which is a common symptom of anemia, can have detrimental effects on a person's quality of life and determine the onset of depressive symptoms (15,16).

An alternative explanation to our findings is that the link between anemia and depression is caused by underlying disease. Although restricted analyses among healthier participants did not change our results, we can not rule out that (unmeasured) diseases affected our results.

The prevalence of depression in our study is higher compared with other observations. A possible explanation for this finding is the low socioeconomic status of this population (as suggested by the low educational status of participants in this study), a factor that has been directly associated with depression (37). However, the prevalence of depression in this study did not differ substantially from that observed in a general population in Northern Italy (38).

Depressive symptoms have been associated with vitamin B12 deficiency, a factor potentially related to anemia (39). Therefore, we repeated the analysis after excluding cases of anemia related to vitamin B12 deficiency, and achieved results similar to those from the whole sample.

The present study has several limitations. We did not explicitly determine the underlying cause of anemia. Therefore, we may have missed the presence of some other diseases or factors such as liver or pancreatic disease, inflammatory bowel disease, and pernicious anemia, which could have explained some of the findings. In addition, although we adjusted all analyses for several potential confounders, including common chronic conditions, it is possible that anemia is simply an indicator of poor health status, and that its association with depression is illustrative of that. Finally, because of the cross-sectional design of the study, we were not able to identify a causal relationship between anemia and depression.

Conclusion

Our findings indicate that depression, possibly independent of its underlying cause, is associated with anemia in a general population of older persons living in the community. Future longitudinal studies should confirm and explain the reason for this association.

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