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Depression, antidepressants and low hemoglobin level in the Paris Prospective Study III: A cross-sectional analysis

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ABSTRACT

Anemia is known to be associated with depression both in community and clinical populations. However, it is still unknown if this association depends or not on antidepressant intake. We investigated the respective association of depression and antidepressant intake with low hemoglobin level in a large community-based cohort. In 8640 volunteers aged 50 to 75 recruited between June 2008 and June 2012 in Paris (France), we assessed hemoglobin levels (g/dl), depressive symptoms and antidepressant intake. We examined the association of both depression and antidepressant intake with hemoglobin level, adjusting for numerous socio-demographic and health variables. We also assessed the association with specific antidepressant classes. Depression and antidepressant intake were independently associated with lower hemoglobin level ($\beta = -0.074$; $p = .05$ and $\beta = -0.100$; $p = .02$ respectively in the fully-adjusted model). Regarding antidepressant classes, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) intake were associated with lower hemoglobin level ($\beta = -0.11$; $p = .01$). To conclude, both depression and antidepressant intake were associated with lower hemoglobin level. In particular, as SSRI or SNRIs intake was also related to lower hemoglobin level, these classes should be used with caution in depressed individuals at risk for anemia.

1. Introduction

Depression has been associated with anemia in several cross-sectional and longitudinal studies in both the clinical and the community settings (Onder et al., 2005; Den Elzen et al., 2009; Hamer and Molloy, 2009; Steptoe et al., 2012). In a previous study, we found that, in adults from the community free of chronic disease, depression was associated with anemia even after accounting for numerous socio-demographic and health-related variables (Vulser et al., 2016).

Although the mechanisms of this association remain unexplained, several hypotheses have been suggested. Shared vulnerability factors, such as vitamin deficiency, may contribute to both anemia and depression. It has also been suggested that anemia could mimic some depressive signs, such as fatigue (Irwin and Miller, 2007). In contrast, depression may lead to lower hemoglobin level through poorer health behaviors, such as alcohol intake or malnutrition (Mitrache et al., 2001; Ng et al., 2009; Quirk et al., 2013; Gaye et al., 2016). Another possible mediating factor between depression and anemia could be the use of psychotropic treatments, notably selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Indeed, in previous studies, these medications have been found to be linked with a higher risk of abnormal bleeding potentially leading to anemia (De Abajo et al., 1999; De abajo and García-Rodríguez, 2008; Andrade et al., 2010; Lindqvist et al., 2014).

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Conversely, one may argue that antidepressants might also reduce the risk of anemia. In preclinical studies, Tryptophan hydroxylase 1-knockout mice deficient in peripheral serotonin display low hemoglobin level (Amireault et al., 2011; Amireault et al., 2013). Moreover, after serotonin supplementation, an increase in erythropoiesis was observed (Amireault et al., 2011; Amireault et al., 2013). Beside their effects on serotonin function, antidepressants might also reduce the risk of anemia by alleviating depressive symptoms resulting in an improvement of health-related behaviors (Mitrache et al., 2001; Ng et al., 2009; Quirk et al., 2013) or by decreasing inflammation or sympathetic tone known to affect erythropoiesis (Cosentino et al., 2015; Maestroni, 2000).

To our knowledge, previous studies that reported an association between low hemoglobin level and depression (Onder et al., 2005; Den Elzen et al., 2009; Hamer and Molloy, 2009; Steptoe et al., 2012; Vulser et al., 2016) did not investigate the possible contribution of antidepressants. Thus, the extent to which depression is associated with low hemoglobin level independently of antidepressants remains unknown.

This large-scale community-based study aimed to investigate the respective association of depressive symptoms and antidepressants with low hemoglobin level. To this aim, we performed a cross-sectional analysis using the baseline data from a large French cohort.

2. Method

2.1. Participants

The Paris Prospective Study 3 (PPS3) is an ongoing observational study on novel markers for cardio-vascular health (Empana et al., 2011). PPS3 participants (N = 10,157, aged 50–75 years) were recruited between June 2008 and June 2012 at the Centre d'Investigations Préventives et Cliniques (IPC), located in Paris (France). The IPC belongs to a network of preventive medical centers that are supported by the French National Insurance System for Salaried Workers to offer a free standardized health check-up every 5 years to all working and retired employees and their families. In addition to a clinical and biological assessment, self-administered questionnaire were used to asses professional activity, lifestyle (smoking and alcohol intake and physical activity), chronic diseases and use of medications. As regards chronic diseases, the participants were required to indicate whether they had a history of hypertension, peripheral artery disease, stroke, myocardial infarction, angina, heart murmur, any other cardiac disease, hepatitis, peptic ulcer, cholelithiasis, intestinal polyp, thyrosis, kidney disease or cancer.

In line with previous studies, participants were excluded from the present study if they had high hemoglobin level ($>$ 15.0 g/dl (9.30 mmol/l) in women and $>$ 16.0 g/dl (9.90 mmol/l) in men) (Ren et al., 2014; Lever-Van Milligen et al., 2014) as they may be at high risk for depressive symptoms (Lever-Van Milligen et al., 2014).

The PPS3 was registered in the World Health Organisation (WHO) International Clinical Trial Registry Platform (NCT00741728) in 25 August 2008. The PPS3 was approved by the local ethics committee and complies with the Declaration of Helsinki. Informed consent of all participants was obtained after having explained all the procedures.

2.2. Assessment of depressive symptoms

Depressive symptoms were measured with the Questionnaire of Depression, Second version, Abridged (QD2A) (Pichot et al., 1984a; Pichot et al., 1984b). This questionnaire consists in 13 items and has been developed especially for the screening depressive symptoms in the community. The QD2A has a high internal consistency (α = 0.91) and a good test-retest reliability in patients with depression (r = 0.84) and in healthy subjects (r = 0.71) (Pichot et al., 1984b). A total score $\geq$ 7 indicates a high probability of having major depressive episode (Pichot et al., 1984a; Pichot et al., 1984b). The QD2A has been recommended by the French National Authority for Health (HAS) for the screening of major depression in primary care (Société de formation thérapeutique du généraliste, Haute Autorité de Santé, 2006) and higher score were associated with higher risk of suicide (Lemogne et al., 2011). In order to improve the interpretability of our results, this cut-off was used to define "depression" in the present study.

2.3. Hemoglobin level

An automated hematology analyzer (ABX Pentra 120) was used to measure hemoglobin level, given in gram/deciliter (g/dl).

2.4. Antidepressant intake

Current medical consumption was checked during a face-to-face interview with a medical doctor. To increase the accuracy of this process, all participants were asked to come to the health examination with their most recent medical prescriptions and/or their medication packages. Only ongoing treatments at the day of the examination were considered. Antidepressants were coded using the WHO Anatomical Therapeutic Chemical (ATC) classification and then classified as SSRIs, SNRIs and other antidepressant drugs (including tricyclic antidepressants, tetracyclic antidepressant (including mirtazapineand mianserin), tianeptine, monoamine oxidase inhibitors and agomelatine. Antidepressants use was categorized in 3 classes: no antidepressant (reference), SSRIs or SNRIs, and other antidepressants. In case of prescription of several antidepressants, participants were included in the SSRIs/SNRIs group if they had at least one prescription of SSRIs or SNRIs and in the other antidepressants group if they had neither a prescription of SSRI nor a prescription of SNRI.

2.5. Covariates

Covariates included sex, age, living status (living alone, with a partner or with family), occupational status, education level, alcohol consumption ($\geq$1 glass/day, $\geq$1 glass/week, $<$ 1 glass/week, never), regular physical activity (yes or no), creatinine clearance, body mass index (BMI), smoking status and chronic disease. Occupational status was categorized into five classes: high, medium, low, unemployed and without a paid occupation participants. Education level was categorized into six status (illiterate, no diploma, lower secondary education, upper secondary education, post-secondary education, bachelor's degree or higher). BMI was calculated using weight and height in meters measured during the health examination and was categorized into the following classes: $<$ 18.5; 18.5–24.99; 25–29.99; $\geq$ 30 kg/m2). Serum creatinine was measured and the Cockcroft-Gault equation was used to calculate the creatinine clearance (in ml/min). Smoking was self-reported and categorized into the following classes: never- ex- and current smoker. Participants were considered as having a chronic disease if they self-reported at least one of the self-reported diseases mentioned above.

2.6. Statistical analyses

We used the version 3.0.2 of the R Statistics software (http://cran.r-project.org) to perform the analyses.

The associations of both depression status and antidepressant intake with hemoglobin level were assessed with general linear models. We first examined the association between depression status (i.e. QD2A $\geq$ 7 or $<$ 7, main exposure) and hemoglobin level (outcome), then between antidepressant intake (co-primary exposure) and hemoglobin level, and finally we examined both depression status and antidepressant intake in the same model. For each analysis, we initially only adjusted for age and sex and then for other socio-demographic variables (i.e., occupational status, living status, and education level) and health variables (i.e. alcohol consumption, physical activity, creatinine clearance, BMI and cigarette smoking) as covariates. Next, we

tested for the presence of an interaction between sex and either depression status or antidepressant intake, and between depression status and antidepressant intake by including corresponding interaction terms.

We further considered four groups to explore the relative effect size and 95% confidence interval of the associations between hemoglobin level and both depression and antidepressants intake: participants who were not depressed (i.e. QD2A < 7) and who did not take antidepressant; participants who were depressed (i.e. QD2A ≥ 7) and who did not take antidepressant; participants who were not depressed and who used antidepressant; and participants who were depressed and who used antidepressant. The association between group and hemoglobin level was examined in age and sex adjusted model and in fully-adjusted model.

To explore the specificity of the association between antidepressant intake and hemoglobin level, the association between antidepressant use classes and hemoglobin level was examined in 3 models: 1) a model adjusted for age and sex, 2) a model adjusted for age, sex, socio-demographic and health variables, and 3) a model adjusted for age, sex, socio-demographic and health variable, and depression status.

Previous analyses were repeated as sensitivity analyses after including participants with high hemoglobin level.

Propensity score analyses were performed to minimize for indication bias for antidepressant prescription (Brookhart et al., 2013). We estimated the propensity of receiving SSRIs or SNRIs using logistic regression analysis with age, sex, other socio-demographic variables, health variables and chronic diseases as covariates on an a priori basis. Propensity score was then used to generate a weight using inverse probability treatment weighting estimation. The weight was then stabilized using truncation (Cole and Hernán, 2008). Stabilized weights are used to increase precision in the estimated treatment effects by reducing the variance of the weights (Brookhart et al., 2013). Then, the relationship between SSRIs/SNRIs use and hemoglobin level was repeated using the truncated weight.

Exploratory analyses were performed to investigate the moderating role of chronic diseases in the association of both depression status and antidepressant intake with hemoglobin level. Since antidepressants may influence hemoglobin level through modulating the risk of bleeding or systemic inflammation, we hypothesized that their association with hemoglobin could be merely observed in participants with a condition associated with a risk of bleeding or increased inflammation, especially cancers. We thus explored the interaction between depression status and self-reported chronic disease (no chronic disease, cancer, other chronic disease) after adjustment for socio-demographic and health variables as well as antidepressant use. A similar model was then performed using the interaction between antidepressants use class and self-reported chronic disease. Should these two interactions be significant, we planned to further examine the association with hemoglobin level in analyses stratified by chronic disease. Finally, we investigated the moderating role of a prescription of treatments known to increase the risk of bleeding in the relationship between antidepressant intake and hemoglobin level. Participants who had a prescription of aspirin, non-steroidal anti-inflammatory drug (NSAID), steroid or anticoagulant were considered as having an at-risk treatment. As for chronic disease, we explored the interaction between antidepressants use class and at-risk treatment in a model adjusted for all socio-demographic and health variables as well as depression status.

3. Results

After study selection, the final sample of the present study included 8640 participants (5077 men, 58.76%) with a mean age (± standard deviation) of 59.63 ± 6.32 years. Study population selection is described in Fig. 1. The mean hemoglobin level was 14.26 ± 1.02 g/dl (women: 13.49 ± 0.81; men: 14.80 ± 0.78). The mean QD2A score was 1.24 ± 2.40 (median: 0.00, interquartile range: 1.00); 5.53% were considered as depressed (QD2A score ≥ 7) (N = 478). Antidepressants were prescribed in 396 participants (4.58%): 317 participants reported a prescription of SSRI (n = 238) and/or SNRI (n = 79) and 79 of another antidepressant. Ten participants with another antidepressant also had a prescription of SSRI and were thus included in the SSRI group. The characteristics of study participants according to depression status and antidepressant intake are displayed in Table 1.

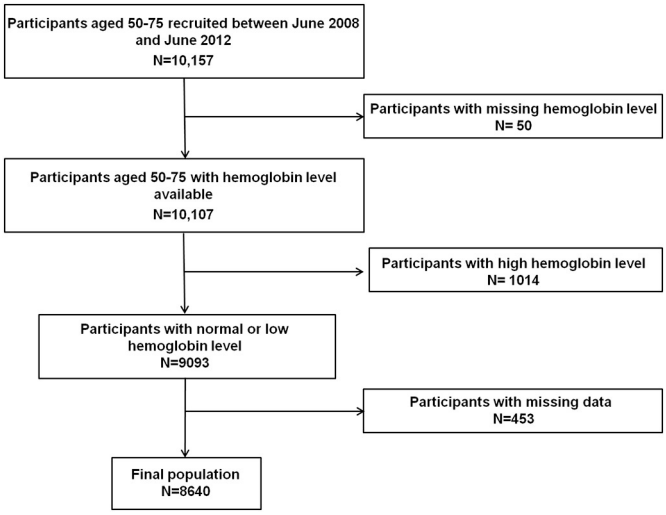

Fig. 1. Flow chart of the study population.

In separate general linear models, after adjustment for age and sex, both depression status and antidepressant intake were associated with lower hemoglobin level (Table 2). These associations remained roughly similar following adjustment for other socio-demographic and health-related variables. These associations only slightly decreased when depression status and antidepressant intake were assessed in the same model indicating that both depression and antidepressants were independently associated with lower hemoglobin level. Interactions with age or sex were not significant in any model (all p > .24). Similarly, there was no significant interaction between depression status and antidepressant intake (p = .73).

Consistently with the linear regression analysis, stratified analysis according to the depression and antidepressant intake status (Table 3) indicates a significant and graded association with hemoglobin level across the groups. In particular, the strongest association was observed in people with depression and antidepressant intake. Briefly, the figures were consistent with a mere additive 'effect' of depression and antidepressant intake on hemoglobin level.

As regards antidepressant classes, SSRIs and SNRIs, but not other antidepressants, were associated with lower hemoglobin level (Table 4).

Sensitivity analyses including participants with high hemoglobin level revealed that antidepressant intake, and particularly SSRIs and SNRIs, were still associated with lower hemoglobin levels with similar effect size as in the main analysis. In contrast, the effect size associated with depressive symptoms decreased and was no longer significant (Supplemental Tables).

In propensity score weighting analysis, both SSRIs/SNRIs use (β = −0.352; p < .001) and depression (β = −0.307; p < .001) were associated with lower hemoglobin.

Finally, in exploratory analyses there was no significant interaction between depression status and chronic disease (p = .69), suggesting that depression was associated with lower hemoglobin level regardless of chronic disease. In contrast, we observed a significant interaction between antidepressant intake and chronic disease (p = .048) due to a significant interaction between SSRIs/SNRIs use and cancer. In stratified analyses, SSRIs/SNRIs use was associated with lower hemoglobin

Table 1
Characteristics of study participants (N = 8640) by depression status and antidepressants intake.

	Depression status				p	Antidepressants intake				
	QD2A score < 7		QD2A score ≥ 7			No		Yes		
	N = 8162		N = 478			N = 8244		N = 396		p
Continuous variables	Mean	sd	Mean	sd		Mean	sd	Mean	sd	
Age (years)	59.66	6.33	59.05	6.18	0.04	59.59	6.31	60.44	6.51	0.01
QD2A score (0−13)	0.78	1.41	9.19	1.85	< 0.001	1.13	2.23	3.57	4.03	< 0.001
Hemoglobin level (g/dl)	14.29	1.01	13.84	1.05	< 0.001	14.28	1.02	13.81	1.00	< 0.001
Mean corpuscular volume (fL)	92.50	4.63	92.40	5.14	0.70	92.50	4.68	93.10	4.24	0.003
Serum creatinine level (μmol/L)	79.90	14.60	74.80	13.00	< 0.001	79.80	14.80	75.20	13.30	< 0.001
Creatinine clearance (ml/min)	85.03	20.22	83.11	20.15	0.04	85.08	20.21	81.61	20.17	< 0.001
Discrete variables	N	%	N	%		N	%	N	%	
Depression status					-					< 0.001
Depressed (QD2A ≥7)	0	0	478	100		382	4.63	96	24.24	
Non-depressed (QD2A < 7)	8162	100	0	0		7862	95.37	300	75.76	
Antidepressant intake					< 0.001					-
SSRIs	182	2.22	56	11.72		0	0	238	60.10	
SNRIs	54	0.66	25	5.23		0	0	79	19.95	
Other antidepressants	64	0.78	15	3.14		0	0	79	19.95	
No antidepressant	7862	96.32	382	79.92		8244	100	0	0	
Sex					< 0.001					< 0.001
Men	4919	60.27	158	33.05		4953	60.08	272	68.69	
Women	3243	39.73	320	66.95		3291	39.92	124	31.31	
Living status					< 0.001					
Living alone	2090	25.61	237	49.58		2175	26.38	152	38.38	
In couple	5813	71.22	227	47.49		5808	70.45	232	58.59	
With family	259	3.17	14	2.93		261	3.17	12	3.03	
Occupational status					< 0.001					< 0.001
High	3355	41.11	128	26.78		3356	40.70	127	32.07	
Medium	3346	40.99	225	47.07		3384	41.05	187	47.22	
Low	465	5.70	25	5.23		476	5.77	14	3.54	
Unemployed participants	655	8.02	73	15.27		688	8.35	40	10.10	
Unpaid occupation	341	4.18	27	5.64		340	4.12	28	7.07	
Education level					< 0.001†					0.88†
Bachelor's degree or higher	3248	4.02	119	24.90		3218	39.03	149	37.63	
Post-secondary education	946	11.59	50	10.46		952	11.55	44	11.11	
Upper secondary education	1448	17.74	98	20.50		1466	17.78	80	20.20	
Lower secondary education	2048	25.09	157	32.85		2103	25.51	102	25.58	
No diploma	437	5.35	49	10.25		466	5.65	20	5.05	
Illiterate	35	0.43	5	1.05		39	0.47	1	0.25	
Alcohol intake					< 0.001					0.02
Never	974	11.93	101	21.13		1008	12.23	67	16.92	
< 1 glass/week	2714	33.25	164	34.31		2738	33.21	140	35.35	
≥1 glass/week and < 1/day	2422	29.67	123	25.73		2441	29.61	104	26.26	
≥1 glass/day	2052	25.14	90	18.83		2057	24.95	85	21.46	
Body mass index					< 0.001					0.02
< 18.5	140	1.72	18	3.77		147	1.78	11	2.78	
18.5–24.99	4156	50.92	231	48.33		4194	50.87	193	48.74	
25–29.99	3156	38.67	162	33.89		3177	38.54	141	35.61	
> 30	710	8.70	67	14.02		726	8.81	51	12.88	
Smoking status					< 0.001					< 0.001
Non-smoker	4270	52.32	239	50.00		4327	52.49	182	45.96	
Ex-smoker	2768	33.91	106	22.18		2770	33.60	131	33.08	
Current smoker	1124	13.77	133	27.84		1147	13.91	83	20.96	
Regular physical activity					< 0.001					0.12
Yes	6605	80.92	247	51.67		6646	80.61	306	77.27	
No	1557	19.08	131	27.41		1598	19.39	90	22.73	

QD2A = Questionnaire of Depression 2nd version, Abridged; sd = standard deviation; p = p value for t-tests (continuous variables) and chi-square tests (discrete variables); † = p value for Fisher test.

level in participants with a history of cancer (n = 27 SSRIs/SNRIs users among n = 588 participants with a history of cancer; β = −0.427; p = .003). In contrast, the association was not significant in participants with other chronic diseases (n = 101 SSRIs/SNRIs users among n = 2412 participants with other chronic diseases; β = −0.118; p = .14) or in those free of any chronic disease (i.e. including cancer, n = 178 SSRIs/SNRIs users among n = 5640 participants free of any chronic disease; β = −0.034; p = .58). There was no significant interaction between antidepressant prescription and treatments known to increase the risk of bleeding (p = .83).

4. Discussion

This study aimed to examine simultaneously the cross-sectional association of depression and antidepressants intake with hemoglobin level. To our knowledge, the present study is the first large population-based study addressing this question. After adjusting for socio-demographic and health variables, we found an independent association of both depression and antidepressant intake with lower hemoglobin level in adults aged 50–75 years. As regards antidepressants, lower hemoglobin level was found in participants using SSRIs or SNRIs, but not other antidepressants. These findings were consistent after controlling

Table 2
Associations of depression and antidepressant intake with hemoglobin level in multivariate models (N = 8640).

	Adjustment for age and sex				Multi-adjusted models[a]				Depression and antidepressant intake examined in the same model†	
	Independent variable: Depression status		Independent variable: Antidepressant intake		Independent variable: Depression status		Independent variable: Antidepressant intake			
Group	β [IC 95%]	*p*	β [IC 95%]	*p*	β [IC 95%]	*p*	β [IC 95%]	*p*	β [IC 95%]	*p*
Independent variables										
Depression status	−0.092 [−0.166; −0.019]	0.01	_	_	−0.089 [−1.628; −0.015]	0.01	_	_	−0.074 [−0.149; 0.001]	0.05
Antidepressant intake	_	_	−0.101 [−0.181; −0.021]	0.01	_	_	−0.113 [−0.193; −0.033]	0.006	−0.100 [−0.181; −0.019]	0.02
Covariates										
Age (years)	−0.001 [0.004; 0.001]	0.29	−0.001[−0.004; 0.001]	0.35	−0.002 [−0.005; 0.001]	0.18	−0.002 [−0.005; 0.001]	0.22	−0.002 [−0.005; 0.001]	0.20
Sex										
Women	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Men	1.302 [1.268; 1.337]	< 0.001	1.303 [1.268; 1.337]	< 0.001	1.26 [1.216; 1.299]	< 0.001	1.256 [1.214; 1.298]	< 0.001	1.25 [1.211; 1.295]	< 0.001
Living status										
Living alone	_	_	_	_	Ref	Ref	Ref	Ref	Ref	Ref
In couple	_	_	_	_	0.04 [0.000; 0.079]	0.05	0.042 [0.003; 0.082]	0.04	0.039 [0.000; 0.079]	0.05
With family	_	_	_	_	−0.006 [−0.154; 0.094]	0.91	−0.003 [−0.103; 0.096]	0.95	−0.006 [−0.105; 0.094]	0.91
Occupational status										
High	_	_	_	_	Ref	Ref	Ref	Ref	Ref	Ref
Medium	_	_	_	_	−0.022 [−0.064; 0.021]	0.32	−0.021 [−0.063; 0.021]	0.39	−0.021 [−0.063; 0.021]	0.33
Low	_	_	_	_	−0.129 [−0.211; −0.047]	0.002	−0.127 [−0.209; −0.046]	0.004	−0.129 [−0.210; −0.047]	0.002
Unemployed participants	_	_	_	_	0.031 [−0.057; 0.120]	0.49	0.033 [−0.056; 0.121]	0.37	0.033 [−0.056; 0.121]	0.47
Unpaid occupation	_	_	_	_	−0.076 [−0.141; −0.012]	0.02	−0.078 [−0.142; −0.014]	0.01	−0.076 [−0.140; −0.011]	0.02
Education level										
Bachelor's degree or higher	_	_	_	_	Ref	Ref	Ref	Ref	Ref	Ref
Post-secondary education	_	_	_	_	0.046 [−0.011; 0.102]	0.11	0.044 [−0.012; 0.101]	0.12	0.044 [−0.012; 0.101]	0.12
Upper secondary education	_	_	_	_	0.042 [−0.008; 0.091]	0.10	0.040 [−0.010; 0.096]	0.11	0.041 [−0.008; 0.090]	0.10
Lower secondary education	_	_	_	_	0.052 [0.004; 0.099]	0.03	0.048 [0.000; 0.096]	0.05	0.050 [0.002; 0.098]	0.04
No diploma	_	_	_	_	−0.019 [−0.099; 0.061]	0.64	−0.025 [−0.105; 0.054]	0.53	−0.021 [−0.101; 0.059]	0.60
Illiterate	_	_	_	_	0.048 [−0.202; 0.297]	0.71	0.038 [−0.212; 0.287]	0.77	0.043 [−0.206; 0.293]	0.73
Alcohol intake										
Never	_	_	_	_	Ref	Ref	Ref	Ref	Ref	Ref
< 1 glass/week	_	_	_	_	0.161 [0.101; 0.222]	< 0.001	0.162 [0.102; 0.222]	< 0.001	0.160 [0.100; 0.221]	< 0.001
≥1 glass/week and < 1/day	_	_	_	_	0.144 [0.087; 0.202]	< 0.001	0.145 [0.087; 0.203]	< 0.001	0.143 [0.086; 0.201]	< 0.001
≥1 glass/day	_	_	_	_	0.119 [0.063; 0.175]	< 0.001	0.120 [0.065; 0.176]	< 0.001	0.118 [0.063; 0.174]	< 0.001
Body mass index										
< 18.5	_	_	_	_	−0.198 [−0.324; −0.071]	0.002	−0.200 [−0.327; −0.074]	0.002	−0.198 [−0.325; −0.072]	0.002
18.5–24.99	_	_	_	_	Ref	Ref	Ref	Ref	Ref	Ref
25–29.99	_	_	_	_	0.104 [0.064; 0.143]	< 0.001	0.104 [0.065; 0.144]	< 0.001	0.105 [0.065; 0.144]	< 0.001

(*continued on next page*)

Table 2 (*continued*)

	Adjustment for age and sex		Multi-adjusted models[a]		Depression and antidepressant intake examined in the same model[†]
	Independent variable: Depression status	Independent variable: Antidepressant intake	Independent variable: Depression status	Independent variable: Antidepressant intake	
> 30	-	-	0.186 [0.116; 0.256]	< 0.001	0.188 [0.118; 0.258]	< 0.001
Creatinine clearance (ml/min)			0.000 [−0.001; 0.001]	0.87	0.000 [−0.001; 0.001]	0.87
Smoking status						
Non-smoker	-	-	Ref	Ref	Ref	Ref
Ex-smoker	-	-	−0.004 [−0.042; 0.034]	0.83	−0.003 [−0.041; 0.035]	0.89
Current smoker	-	-	0.111 [0.060; 0.163]	< 0.001	0.044 [0.063; 0.166]	< 0.001
Regular physical activity						
No	-	-	Ref	Ref	Ref	Ref
Yes	-	-	0.008 [−0.035; 0.050]	0.72	0.009 [−0.035; 0.050]	0.69

SSRIs = Selective serotonin reuptake inhibitors.
SNRIs = Serotonin-norepinephrine reuptake inhibitors.
β [IC 95%] = Estimated parameter, 95% confidence intervals.
p = p value.
Ref = Reference group.
[a] Adjustment for age, sex, living status, occupational status, education level, alcohol intake, regular physical activity, creatinine clearance, body mass index and smoking status.

for indication bias with propensity scores. Also, exploratory analysis suggests a strong association between SSRIs/SNRIs and lower hemoglobin level in participants with a history of cancer. In contrast, depression was associated with lower hemoglobin level regardless of chronic disease.

This study confirms and extents results from previous ones showing an association between depression and low hemoglobin level (Onder et al., 2005; Den Elzen et al., 2009; Hamer and Molloy, 2009; Steptoe et al., 2012; Vulser et al., 2016). As in our previous study, this association only slightly decreases and remains significant after adjustment for numerous socio-demographic and health variables (Vulser et al., 2016). But the most important finding of this study is that the association between depression and lower hemoglobin level was independent of antidepressant intake. Indeed, we observed that this association remained qualitatively similar after further adjustment for antidepressant intake. Sensitivity analyses including participants with high hemoglobin levels revealed that antidepressant intake, and particularly SSRIs and SNRIs, were still associated with lower hemoglobin levels with similar effect size as in the main analysis. In contrast, the association between depressive symptoms and hemoglobin levels decreased, as expected, supporting the previously reported association between depressive symptoms and high hemoglobin levels (Lever-Van Milligen et al., 2014).

Showing no interaction between depression and antidepressants, the present results are rather consistent with a solely additive effect of depression and antidepressants intake on lower hemoglobin level. Indeed, depression without antidepressants intake and antidepressants intake without depression were associated with lower hemoglobin to a similar extent. Furthermore, the magnitude of the association observed in participants with both depression and antidepressants could be expected from the mere addition of two independent effects. This result does not support the hypothesis that antidepressants may reduce the risk of low hemoglobin level, whatever the mechanism (improving depressive symptoms, increasing serotonin level or decreasing inflammation). Indeed, as reported in the introduction, in vitro studies have observed higher erythropoiesis after serotonin supplementation (Amireault et al., 2011; Amireault et al., 2013). Thus, antidepressant, and notably SSRIs and SNRIs would have been associated with higher hemoglobin level. However, no study has addressed this effect in humans. Furthermore, the effects of antidepressants may differ from serotonin supplementation. Considering inflammation, numerous studies have reported a significant role of antidepressants on the pro−/anti-inflammatory cytokines balance that would lead to decrease inflammation. However, a recent meta-analysis showed no effect of antidepressant on interferon-γ (INF-γ) (Wiedlocha et al., 2018), a cytokine that is involved in anemia of inflammation through induction of the indoleamine (2,3)-dioxygenase pathway (Weiss et al., 2004).

In contrast, we observed an association between SSRIs or SNRIs intake and lower hemoglobin level. This association was independent of depression status. To our knowledge, such an association had never been reported in the general population. Only one study reported that the use of SSRIs during pregnancy was likely to double the risk of post-partum anemia (Lindqvist et al., 2014). However, several studies have reported that SSRIs or SNRIs intake was associated with a higher risk of bleeding potentially leading to lower hemoglobin level. Thus, SSRIs and SNRIs are known to increase the risk of gastrointestinal bleeding partly due to an increase in gastric acid secretion (De Abajo et al., 1999; De abajo and García-Rodríguez, 2008; Andrade et al., 2010). In women, taking SSRIs during pregnancy has also been found to double the risk of post-partum hemorrhage (Lindqvist et al., 2014; Grzeskowiak et al., 2016). Such increased risk of bleeding may be explained by changes in hemostasis activity induced by SSRIs. The activity of serotonin-reuptake transporters of the platelets is decreased by SSRIs and SNRIs, leading to a lower amount of serotonin available in the platelets which in turn leads to an alteration of the coagulation cascade and a prolongation of bleeding time (Halperin and Reber, 2007). In the literature, such an

Table 3
Linear regression analysis of hemoglobin level (dependant variable) according to the depression and antidepressant intake status (N = 8640).

		Model adjusted for age and sex			Multi-adjusted model[a]		
Group	N	β	95% CI	*p*	β	95% CI	*p*
No depression and no antidepressant intake	7862	Ref	Ref	Ref	Ref	Ref	Ref
Depression and no antidepressant intake	382	−0.084	[−0.166; −0.002]	0.04	−0.080	[−0.162; −0.002]	0.06
No depression and antidepressant intake	300	−0.093	[−0.184; −0.001]	0.05	−0.107	[−0.198; −0.016]	0.02
Depression and antidepressant intake	96	−0.147	[−0.307; −0.012]	0.07	−0.152	[−0.311; −0.006]	0.06

β = estimated parameter; 95% CI = 95% confidence interval; *p* = *p* value; ref = reference group.
[a] Adjustment for age, sex, living status, occupational status, education level, alcohol intake, regular physical activity, creatinine clearance, body mass index and smoking status.

effect has been found to be enhanced when taken with NSAIDs or aspirin (Dalton et al., 2006; Labos et al., 2011; Meijer et al., 2004). However, in our study, we did not find any interaction effect between antidepressants intake and treatments known to increase the risk of bleeding. Other antidepressants, by their influence on serotonin transmission and levels might also have hemostasis effects. However, their lower degree of serotonin reuptake inhibition may explain why such an effect has not been observed in our study or reported in the literature (Meijer et al., 2004).

In exploratory analyses, we observed that the association between SSRIs/SNRIs intake and lower hemoglobin level was particularly marked in participants reporting a history of cancer. To our knowledge, this association has never been reported specifically in individuals with cancer, or history of cancer. Cancers could decrease hemoglobin level through iron deficiency, nutritional status, inflammation or side effects of chemotherapy (Groopman and Itri, 1999; Kraft et al., 2014). In patients with cancer, it might be possible that SSRIs/SNRIs interact with such biological mechanism or with chemotherapy (Kraft et al., 2014). In the present study, the date of diagnosis and type of cancer, its stage or the date and type of treatment received were not available at baseline examination so that these results should be interpreted with caution. Should the association between SSRIs/SNRIs and lower hemoglobin level in patients with cancer be replicated, further studies will thus be required to investigate its underlying mechanisms.

Strengths of the present study include the size of the sample, the community-based nature of the population, the relatively large number of potential confounders and the possibility to simultaneously investigate depressive symptoms and antidepressant intake, which was carefully ascertained by an interview with a medical doctor. This study also presents some limitations. First, due to the cross-sectional design of the present study, it is not possible to infer causal directions in the observed associations. Second, details about cancer were not assessed in participants reporting such history. Third, depression symptoms were self-reported and not searched for with a standardized interview so that major depression was not formally diagnosed. The present study took advantage of the data collected during the free, standardized health check-up implemented in the IPC. This check-up includes the QD2A as a tool for screening for depression in the general population, as recommended by the French National Authority for Health (HAS) (Société de formation thérapeutique du généraliste, Haute Autorité de Santé, 2006). Therefore, we had no choice but to use this scale. Although the QD2A has demonstrated its ability to screen for depressive episodes in healthy subjects (Pichot et al., 1984a; Pichot et al., 1984b), it has never been translated in English, thus limiting its use worldwide. In addition, since only one time point was available, our study might have underestimated the association between depressive symptoms and low hemoglobin level because of transient symptoms in some participants. Fourth, exploratory analysis on chronic diseases should be considered as hypotheses generated and be confirmed in specific studies. Fifth, although current medication consumption was checked by a medical doctor, it cannot be verified with certainty that participants had taken antidepressants.

Our results suggest that, in adults aged 50–75 years from the general population, the association between depression and anemia is independent of antidepressant intake. Antidepressants are not likely to improve hemoglobin level in patients with depression. In contrast, SSRIs and SNRIs were associated with lower hemoglobin level, and should thus be used with caution in depressed individuals at risk for anemia, notably patients with a history of cancer. This knowledge may help guide therapeutic measures for depressed individuals at risk for anemia.

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Table 4
Associations between antidepressant classes and hemoglobin level in multivariate models (*N* = 8640).

		Model adjusted for age and sex			Multi-adjusted model[a]			Further adjustment for depression[b]		
Group	N	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
No antidepressant intake	8244	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SSRIs or SNRIs	317	−0.110	[−0.199; −0.021]	0.02	−0.126	[−0.215; −0.037]	0.005	−0.112	[−0.203; −0.023]	0.01
Other antidepressants	79	−0.064	[−0.240; 0.111]	0.47	−0.057	[−0.232; 0.116]	0.52	−0.048	[−0.223; 0.126]	0.59

SSRIs = Selective serotonin reuptake inhibitors.
SNRIs = Serotonin-norepinephrine reuptake inhibitors.
β = Estimated parameter; 95% CI = 95% confidence interval; *p* = *p* value; Ref = Reference group.
[a] Adjustment for age, sex, living status, occupational status, education level, alcohol intake, regular physical activity, creatinine clearance, body mass index and smoking status.
[b] Adjustment for depression status, age, sex, living status, occupational status, education level, alcohol intake, regular physical activity, creatinine clearance, body mass index and smoking status.

CRediT authorship contribution statement

Hélène Vulser:Conceptualization, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing.**Cédric Lemogne**:Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing - original draft, Writing - review & editing.**Pierre Boutouyrie**:Visualization, Writing - review & editing.**Francine Côté**:Conceptualization, Visualization, Writing - review & editing.**Marie-Cécile Perier**:Data curation, Methodology, Software, Visualization, Writing - review & editing.**Thomas Van Sloten**:Visualization, Writing - review & editing.**Nicolas Hoertel**:Visualization, Writing - review & editing.**Nicolas Danchin**:Visualization, Writing - review & editing.**Frédéric Limosin**:Visualization, Writing - review & editing.**Xavier Jouven**:Visualization, Writing - review & editing.**Jean-Philippe Empana**:Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

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