Journal of Psychosomatic Research 76 (2014) 317–321

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Hemoglobin levels in persons with depressive and/or anxiety disorders

Bianca A. Lever-van Milligen [a,*], Nicole Vogelzangs [a], Johannes H. Smit [a], Brenda W.J.H. Penninx [a,b,c]

[a] Department of Psychiatry, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands
[b] Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands
[c] Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 25 September 2013
Received in revised form 13 January 2014
Accepted 20 January 2014

Keywords:
Depression
Anxiety
Hemoglobin
Anemia

ABSTRACT

Objective: Both low and high hemoglobin levels lead to more physical diseases, and both are linked to mortality. Low hemoglobin, often classified as anemia, has also been linked to more depressive symptoms, but whether both hemoglobin extremes are associated with depressive disorder and potentially also with anxiety disorder has not been examined before. This study examines to which extent hemoglobin levels are associated with depression and anxiety disorders in a large cohort.
Methods: The study sample consisted of 2920 persons from the Netherlands Study of Depression and Anxiety. Hemoglobin levels were determined after venipuncture. Depressive and anxiety disorders were determined according to a DSM-IV-based psychiatric interview. Clinical psychiatric characteristics included the severity of depression and anxiety, the duration of symptoms, the age of onset and the antidepressant use.
Results: Higher hemoglobin levels were found in those with current depressive and/or anxiety disorders after sociodemographic adjustment and both higher, and lower hemoglobin levels were found in persons with higher depression and anxiety severity. However, after full adjustment for sociodemographics, disease indicators and lifestyle, associations were no longer significant.
Conclusions: This cohort study showed that there is no independent association between depressive and/or anxiety disorders and hemoglobin levels or anemia status.

Introduction

Extreme hemoglobin levels (Hb), both low and high levels, lead to deteriorated quality of life [1,2], have been associated with greater mortality in elderly persons [2,3] and have been linked to the development of diseases, such as heart failure or cardiovascular diseases (for low hemoglobin levels) [4,5] and hypertension or thrombosis (for high hemoglobin levels) [6].

Beyond these physical health problems, previous research has shown that low hemoglobin level (anemia) is associated with more depressive symptoms [7–11]. Such an association could be expected since symptoms of low hemoglobin level (paleness, fatigue, dizziness, shortness of breath during physical activity, higher heart beat in resting state and heart fluttering) also often occur when having depressive (or anxiety) symptoms. This association between low hemoglobin level and depression could potentially be explained by underlying poorer physical health status such as fatigue [12–14], reduced levels of brain oxygen [15], vitamin B12 deficiency [16–18] or higher inflammatory levels [19–21]. Earlier studies on anemia and depression included elderly or diseased persons only and did generally not consider the presence of psychiatric disorders but used self-report measures of depressive symptomatology. Consequently, whether low hemoglobin levels are associated with psychiatric depression in a younger adult sample needs to be clarified. In addition, whether an association between anemia and mental health extends to anxiety disorders, a highly comorbid condition to depression with partly shared pathophysiology, needs to be established as well. Furthermore, whether high hemoglobin levels are also associated with depressive and anxiety disorders has not been examined before. Such an association could be expected since both high hemoglobin and depressive and anxiety disorders are associated with vascular disease [6,22,23] and smoking [24,25] probably due to increased blood viscosity [26].

This cohort study examines the association between hemoglobin levels and the presence of depressive and anxiety disorders in an adult population. Both the low end and the high end of the hemoglobin spectrum will be distinguished, considering the fact that both ends have been associated with poorer health. We also examined whether an association between low or high hemoglobin levels and psychiatric disorders is dependent on clinical psychiatric characteristics, such as severity, duration, age of onset of the depressive or anxiety disorder and antidepressant use.

Methods

Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing longitudinal cohort study that investigates the long-term course

* Corresponding author at: A.J. Ernststraat 1187, 1081 HL Amsterdam, The Netherlands. Tel.: +31 20 788 5679.
E-mail address: b.lever@ggzingeest.nl (B.A. Lever-van Milligen).

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http://dx.doi.org/10.1016/j.jpsychores.2014.01.004

and consequences of depressive and anxiety disorders. During a 4-hour measurement, a wide range of data were collected, including the assessment of demographics, a diagnostic psychiatric interview and a medical examination including blood collection. All respondents signed an informed consent. The NESDA protocol was approved by the ethical review board of all participating universities. A total of 2981 respondents, aged 18–65 years, were recruited from the general population (19%), primary care (54%) and mental health care organizations (27%) to represent various settings and stages of psychopathology. General population-based persons had previously participated in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) [27] or the Adolescents at Risk for Anxiety and Depression (ARIADNE) study [28]. The NEMESIS participants were selected when a 12-month recency diagnoses of depressive or anxiety disorder was met at baseline or during follow-up. A total of 776 participants of NEMESIS were selected and 662 were approached. Of these, 303 persons were willing to participate in NESDA. The ARIADNE participants ($N = 528$) were asked for participating in NESDA when they did not have a CIDI diagnosis of excluding psychiatric diagnoses, were fluent in Dutch and were willing to participate in NESDA ($N = 261$). Primary care patients were identified through a three-stage screening procedure. Screening questionnaires were sent to a random sample of 23750 patients aged 18–65 years who consulted their general practice in the last 4 months irrespective of reason for consultation. The screening questionnaire consisted of the Kessler-10 [29] with proven qualities for affective disorders. A screen-positive score on the K-10 was defined as a validated K-10-score of ≥20 or a positive score on one of the five added anxiety questions. A total of 10,706 persons returned the screener and 4887 were screen-positive. These persons were approached for a short phone-screen interview consisting of the CIDI-short form sections of depression and anxiety. Those who fulfilled the CIDI-short form criteria for a current depressive or anxiety disorder during the phone-screen and who were not treated for psychiatric conditions in a psychiatric mental health care setting were invited to participate in the NESDA study. A total of 743 participants with a current (6 months recency) and 353 participants with a non-current depressive or anxiety disorder were recruited, as well as 141 persons with subthreshold symptoms (screen-positives not fulfilling diagnostic criteria). Furthermore, a random selection of the screen-negatives (both from the written screen and the phone screen) also participated (373 participants) and constituted a 'healthy control group'. Mental health care patients were recruited when newly enrolled in the participating mental health organizations with a primary depressive or anxiety diagnoses ($N = 1597$). Of those, 807 persons with a current depressive or anxiety disorder were willing to participate in NESDA. Exclusion criteria for the NESDA study were not speaking Dutch and a known primary clinical diagnosis of bipolar disorder, obsessive–compulsive disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder. A description of the rationales, methods and recruitment strategy is reported elsewhere [30].

To evaluate the association between hemoglobin levels and depression and anxiety, persons with missing hemoglobin levels were excluded ($N = 61$), resulting in a sample of 2920 persons consisting of healthy controls (22%) and patients with depressive and/or anxiety disorders (78%). No significant differences in basic characteristics (age, sex and years of education) were found between included and excluded persons.

Hemoglobin levels

Fasting blood samples were drawn early in the morning using venipuncture. On the same day, blood was sent to the laboratory where hemoglobin levels were determined using standard laboratory methods. Anemia was defined according to the World Health Organization (WHO) criteria as a hemoglobin (Hb) concentration <12 g/dl (7.5 mmol/l) in women and <13 g/dl (8.1 mmol/l) in men. High hemoglobin level was determined following the literature [2,3] as a hemoglobin level ≥3.1 g/dl above the cutoff value of anemia (women: ≥15.1 g/dl (9.3 mmol/l) and men: ≥16.1 g/dl (9.9 mmol/l)). As suggested by earlier studies [12,13,31], a categorical variable of hemoglobin was created so that the association between both low and high hemoglobin level could be examined: (1) Hb below the anemia cutoff (anemia); (2) Hb level: 0.1–2 g/dl above anemia cutoff (reference group, considered as optimal Hb levels based on earlier studies); (3) Hb level: 2.1–3 g/dl above anemia cutoff (slightly increased hemoglobin level); and (4) Hb level: ≥3.1 g/dl above anemia cutoff (high hemoglobin level).

Diagnoses of depressive and anxiety disorders

Depressive disorders (including major depressive disorder and dysthymic disorder) and anxiety disorders (including social phobia, panic disorder, agoraphobia and generalized anxiety disorder) were established using the Composite International Diagnostic Instrument (CIDI, WHO version 2.1) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). The CIDI is a valid and reliable instrument to assess depressive and anxiety disorders [32] and was administered by specially trained research staff. Participants were categorized as lifetime healthy controls ($N = 640$), remitted depressive and/or anxiety disorders ($N = 614$) and current (6-month recency) depressive and/or anxiety disorders ($N = 1666$). Depressive and anxiety disorders were analyzed together since they largely share same pathophysiology and since there was a high percentage of comorbidity (60%) in this sample.

Clinical psychiatric characteristics of depressive and anxiety disorders

Several clinical characteristics of depressive and anxiety disorders were selected to explore whether specific aspects are associated with hemoglobin levels. The severity of depression was measured with the Inventory of Depressive Symptoms (IDS, a 30-item self-report questionnaire [33]). The severity of anxiety was measured with the Beck Anxiety Inventory (BAI, a 21-item self-report questionnaire [34]). Antidepressant use was determined through drug container inspection of all drugs used in the past month and classified according to the Anatomical Therapeutic Chemical (ATC) classification: tricyclic antidepressants (ATC-code N06AA), selective serotonin re-uptake inhibitors (ATC-code N06AB) and other antidepressants (ATC-code N06AF/N06AX). The duration of depressive and anxiety symptoms was evaluated using the Life Chart method [35], in which the presence of symptoms of depressive and anxiety disorders during 4 years prior to baseline was assessed. The duration of symptoms was expressed as the percentage of time in which symptoms were present. The age of onset was retrospectively derived from the CIDI interview and when multiple disorders were present; the earliest onset was used in the analyses.

Covariates

Sociodemographics included age (in years), sex and education (in years). In addition, various disease indicators and lifestyle characteristics were considered as covariates since these have been linked to both depression/anxiety and hemoglobin levels. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A count of the number of chronic somatic diseases for which a respondent receives treatment (including lung disease, diabetes, cardiovascular disease, cancer, osteoarthritis, intestinal disorder, liver disease, epilepsy and thyroid gland diseases) was made based on self-report. Creatinine clearance in milliliters per minute was used to account for effects of renal function and was calculated using plasma creatinine based on the CKD-EPI formula [36]. Smoking status was defined as current or no current smoker. Alcohol intake was categorized as non-drinking (<1 drink/week), moderate drinking (1–14 (women)/1–21 (men) drinks/week) and heavy drinking (>14 (women)/>21 (men) drinks/week). Physical activity was measured with the International