Psychoneuroendocrinology (2013) 38, 2309—2318

Available online at www.sciencedirect.com

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Association of serum homocysteine with major depressive disorder: Results from a large population-based study

Hermann Nabi [a,b,*], Murielle Bochud [c], Jennifer Glaus [d], Aurélie M. Lasserre [d], Gérard Waeber [e], Peter Vollenweider [e,1], Martin Preisig [d,1]

[a] INSERM, U1018, Centre for Research in Epidemiology and Population Health, Epidemiology of Occupational and Social Determinants of Health, Villejuif F-94807, France
[b] Université de Versailles St Quentin, UMRS 1018, Villejuif F-94807, France
[c] Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[d] Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland
[e] Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne 1011, Switzerland

Received 7 February 2013; received in revised form 23 April 2013; accepted 30 April 2013

KEYWORDS
Homocysteine;
Major depressive disorder;
Population-based study

Summary
Background: Studies on the association between homocysteine levels and depression have shown conflicting results. To examine the association between serum total homocysteine (tHcy) levels and major depressive disorder (MDD) in a large community sample with an extended age range.
Methods: A total of 3392 men and women aged 35—66 years participating in the CoLaus study and its psychiatric arm (PsyCoLaus) were included in the analyses. High tHcy measured from fasting blood samples was defined as a concentration $\geq$15 μmol/L. MDD was assessed using the semi-structured Diagnostic Interview for Genetics Studies.
Results: In multivariate analyses, elevated tHcy levels were associated with greater odds of meeting the diagnostic criteria for lifetime MDD among men (OR = 1.71; 95% CI, 1.18—2.50). This was particularly the case for remitted MDD. Among women, there was no significant association between tHcy levels and MDD and the association tended to be in the opposite direction (OR = 0.61; 95% CI, 0.34—1.08).
Conclusions: In this large population-based study, elevated tHcy concentrations are associated with lifetime MDD and particularly with remitted MDD among men.

* Corresponding author at: INSERM, U1018, Hôpital Paul Brousse/Bâtiment 15/16 Avenue Paul Vaillant Couturier, Villejuif Cedex 94807, France. Tel.: +33 0 1 77 74 74 21; fax: +33 0 1 77 74 74 03.
E-mail address: Hermann.Nabi@inserm.fr (H. Nabi).
[1] [1]Joint last authors.

0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2013.04.018

1. Introduction

Elevated levels of blood total homocysteine (tHcy), a sulphur-based amino acid, have been shown to be associated with an increased risk for cardiovascular disease (CVD) (Welch and Loscalzo, 1998). A meta-analysis of prospective studies found that increments in tHcy concentrations result in a significant increased risk of CVD, coronary heart disease (CHD), and stroke, independently of conventional risk factors (Bautista et al., 2002; Holmes et al., 2011). Adding tHcy to the Framingham risk score strongly improved the prediction of CVD in the Multi-Ethnic Study of Atherosclerosis (MESA) and National Health and Nutrition Examination Survey (NHANES-III) cohorts (Veeranna et al., 2011). However, no major randomized trial has shown homocysteine-lowering therapies to have a major impact on cardiovascular events (Bonaa et al., 2006; Lee et al., 2010), rendering the causality of the tHcy—CVD link uncertain.

In addition to being independent risk factor for CVD, several studies suggested a connection between elevated tHcy levels and psychiatric disorders, particularly depression (Muntjewerff et al., 2006; Refsum et al., 2006; Forti et al., 2010). Accordingly, tHcy has been proposed as a candidate in the pathophysiological mechanism through which depression may influence CVD outcomes (Chellappa and Ramaraj, 2009).

However, the case—control and population-based studies that have examined the association between tHcy levels and depression have produced inconsistent findings. Indeed, some of them have documented an association between tHcy levels and depression (Bjelland et al., 2003; Almeida et al., 2004; Tolmunen et al., 2004; Sachdev et al., 2005; Dimopoulos et al., 2007; Kim et al., 2008; Forti et al., 2010), whereas others did not replicate these findings (Penninx et al., 2000; Tiemeier et al., 2002; Ramos et al., 2004; Kamphuis et al., 2007). Furthermore, these studies had several limitations.

First, the majority of them were conducted in older adults (Morris et al., 2003; Refsum et al., 2006; Almeida et al., 2008; Byers et al., 2010). Accordingly, it remains unclear whether the association between tHcy and depression also exists in younger samples. Second, almost all the studies with positive findings (Bjelland et al., 2003; Almeida et al., 2004; Tolmunen et al., 2004; Sachdev et al., 2005; Dimopoulos et al., 2007; Almeida et al., 2008; Kim et al., 2008; Forti et al., 2010) have applied depression rating scales, rather than structured diagnostic interviews that yield standardized criteria for mental disorders at the diagnostic level. Besides the moderate risk of misclassification of current depressive symptoms (Myers and Weissman, 1980; Eaton et al., 2000), studies that solely employ rating scales can hardly take into account past psychopathology, given that such scales generally only cover recent symptoms. Another shortcoming of previous studies is the incomplete consideration of potential confounding factors, such as vascular risk factors that are known to be associated with both tHcy levels and depression (Katon et al., 2004; Refsum et al., 2006; Rubin et al., 2010). None of the previous studies adjusted for all the main vascular risk factors. For example, Tolmunen et al. (2004) adjusted for smoking and alcohol intake, but not for body mass index, diabetes, hypertention, cholesterol, etc. In sum, the relationship between tHcy with depression is still only partially understood and requires further study.

The objectives of the present study were (1) to explore the association between serum tHcy levels and major depressive disorder in a large population-based sample of men and women with an extended age range; and (2) to examine whether the association between tHcy levels and major depression is independent of behavioural and vascular risk factors after controlling for sociodemographic characteristics.

2. Materials and methods

2.1. Study sample

Data are drawn from the CoLaus (Firmann et al., 2008) and PsyCoLaus (Preisig et al., 2009) studies. Briefly, the CoLaus study based on a sample of 6733 individuals (3544 women and 3189 men) randomly selected from the residents of the city of Lausanne (Switzerland) took place from 2003 to 2006. Its major aims are to determine the prevalence of CVD risk factors and assess potential genetic determinants. The inclusion criteria were: (a) written informed consent and (b) age between 35 and 75 years and (c) Caucasian origin. The Caucasian origin was adopted given the strong genetic orientation if the study. PsyCoLaus is the psychiatric arm of the CoLaus study. All participants of the CoLaus study aged 35—66 years (n = 5535) were systematically invited to also participate in the psychiatric evaluation. A total of 3717 (67%) individuals underwent the psychiatric assessment between 2004 and 2008. After excluding participants with missing data (n = 325), the analytic sample of the present study included 3392 participants. The Institutional Ethics Committee of the Faculty of Medicine of the University of Lausanne approved the CoLaus and the PsyCoLaus studies. All participants signed a written informed consent after having received a detailed description of study objectives.

2.2. Measures

2.2.1. Serum total homocysteine (tHcy)

Participants were invited to attend the outpatient clinic at the Centre Hospitalier Universitaire Vaudois (CHUV) in the morning after an overnight fast for clinical examination. Venous blood samples (50 ml) were drawn for each participant and most clinical chemistry assays were performed by the CHUV Clinical Laboratory on fresh blood samples. Serum tHcy level was determined with high-performance liquid chromatography (Firmann et al., 2008). Maximum inter- and intra-batch CVs were 3.1% and 2.9%, respectively. Elevated serum tHcy was defined as a concentration $\geq$15 μmol/L based on the prevailing agreement in the literature (Malinow et al., 1999; Nygard et al., 1997; Ueland et al., 1993).

2.2.2. Major depressive disorder (MDD)

MDD was assessed using validated French version of the semi-structured Diagnostic Interview for Genetics Studies (DIGS) (Nurnberger et al., 1994). The DIGS was developed by the National Institute of Mental Health (NIMH) Molecular Genetics Initiative in order to obtain a more precise assessment of phenotypes through a wide spectrum of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I criteria. The applied semi-structured interview allows