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

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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.

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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

for the assessment of current and past episodes of MDD. The French translation of the DIGS (Leboyer et al., 1995) was extensively tested and revealed excellent inter-rater reliability (kappa = 0.93) and a slightly lower 6-week test–retest reliability (kappa = 0.62) for MDD (Preisig et al., 1999). In order to also assess algorithmically defined depressive syndromes below the DSM-IV threshold, the one-week duration specification of the original DIGS in the depression screen was removed for the PsyCoLaus study. Interviewers were psychologists or psychiatrists trained over a two-month period.

2.2.3. Covariates

Sociodemographic measures included age, sex, marital status and educational level. Behavioural CVD risk factors were assessed using responses to a standardized questionnaire and categorized as follows: smoking status (never, former and current), alcohol consumption [none, low (1–6 drinks/week), moderate (7–13/week) and high (14+/week)]. Physical activity (none, once a week, and twice a week) was assessed by asking participants "how many times a week do you engage in 20 minutes of physical activity." The following biological CVD risk factors were standardly measured at clinical examination after an overnight fast and included in the analyses as categorical variables: overweight/obesity (BMI $\geq$ 25 kg/m^2 or $\geq$30 kg/m^2), high total cholesterol ($\geq$6.2 mmol/L), high triglycerides ($\geq$2.2 mmol/L), hypertension (systolic and diastolic blood pressures $\geq$140/90 mm Hg or presence of antihypertensive medication), diabetes (fasting plasma glucose $\geq$ 7.0 mmol/L or presence of oral hypoglycaemic or insulin treatment), albuminuria (albumin/creatinine ratio (ACR) > 30 mg/g) (Marti et al., 2011) and self-reported doctor diagnosis of CVD event (yes/no). We also included additional covariates such as current diuretic, and antidepressant use assessed by recording all the prescribed drugs taken by each participant. Finally, participants were asked whether they were taking vitamin supplements (yes/no) on a regular basis. No specific information allowing differentiating intakes of vitamin B6, B11 and B12 was collected.

2.3. Statistical analyses

For comparisons of data on tHcy levels and MDD as a function of sample characteristics, chi-square tests were used. The association between tHcy levels and MDD has been examined using five serially adjusted logistic regression models. The interaction of sex with tHcy in relation to MDD was borderline significant ($p = 0.06$). We consider this interaction to be sufficiently significant to warrant separate analyses by sex, considering the gender differences in depression and tHcy concentrations reported previously (Jacques et al., 1999; Piccinelli and Wilkinson, 2000). In model 1, the sex-specific odds ratios (OR) were adjusted for sociodemographic characteristics. In models 2–4, OR were additionally adjusted for health-related behaviours, biological risk factors and medication/vitamins use, respectively. We adjusted model 5 for all of the covariates outlined above. In order to test the robustness of our findings, we undertook several post hoc analyses. First, we conducted a multinomial logistic regression to examine the association of tHcy levels with remitted and current MDD. Second, we divided tHcy levels into 4 categories (<9 μmol/L, 9–11.9 μmol/L, 12–14.9 μmol/L, and $\geq$15 μmol/L) in order to check for a dose–response relation with MDD as done previously (Bjelland et al., 2003). Third, we stratified the analyses by age groups (<43 y, 43–49 y, 50–57 y, $\geq$58 y) to test for a possible effect modification by age. We considered a result to be statistically significant at $p < 0.05$. Analyses were performed using Stata 12 (StataCorp. College Station, TX, USA).

3. Results

The prevalence of elevated serum tHcy ($\geq$15 μmol/L) was 9.6% in men and 3.2% in women. For MDD, the lifetime prevalence was 31.5% in men and 53.9% in women. Specifically, the prevalence of remitted and current MDD was 25.9% and 5.6%, respectively, in men. The corresponding figures in women were 44.3% and 9.6%. The characteristics of the men and women according to tHcy levels are presented in Table 1. In men, higher tHcy concentrations were associated with older age, current smoking, physical inactivity, overweight/obesity, high total cholesterol and triglycerides, hypertension, diabetes, history of CVD, albuminuria, diuretics and vitamins use (all $p \leq 0.03$). In women, higher tHcy concentrations were associated with older age, lower educational level, not being married, hypertension, diabetes and diuretics use (all $p \leq 0.007$).

The characteristics of the men and women with and without MDD are summarized in Table 2. Compared to their non-depressed counterparts, depressed men were more likely to be younger, with higher educational level, not married, current smokers, overweight or obese, and antidepressants and vitamins users (all $p \leq 0.03$). Depressed women were more likely to be younger, not married, current smokers, physically inactive, and antidepressants users (all $p \leq 0.04$).

Table 3 shows the OR estimating the association between tHcy levels and MDD in men and women. In model 1, when adjustments were made for sociodemographic characteristics, men with elevated tHcy levels had a significantly higher odds of meeting the diagnostic criteria for lifetime MDD (OR = 1.52; 95% CI, 1.52–2.16) compared to those with low tHcy level. After additional serial adjustments for health-related behaviours (model 2), biological risk factors (model 3), diuretics, antidepressants and vitamins use (model 4), and for all aforementioned variables (model 5), the magnitude of this association was increased by 37% and remained statistically significant (fully adjusted OR = 1.71; 95% CI, 1.18–2.50). Among women, there was no significant association between tHcy levels and MDD neither in model 1 (OR = 0.71; 95% CI, 0.41–1.22) nor in subsequent models and the association tended to be in the opposite direction (fully adjusted OR = 0.61; 95% CI, 0.34–1.08).

3.1. Post hoc analyses

First, the semi-structured diagnostic interview used in the present study allowed for the assessment of current and past (remitted) episodes of MDD. As shown in Fig. 1, after adjustment for all potential confounders as in the previous model 5, men with both remitted and current MDD were more likely to have an elevated tHcy level (serum concentration $\geq$ 15 μ‴ mmol/L) than those who had never experienced depression,

Table 1 Baseline characteristics of participants as a function of total homocysteine (tHcy) levels by sex.

	Men				Women			
	Serum total homocysteine (μmol/L)				Serum total homocysteine (μmol/L)			
	Mean (SD)	<15	≥15	*p* value	Mean (SD)	<15	≥15	*p* value
Number (%)		1449 (90.4)	154 (9.6)			1731 (96.8)	58 (3.2)	
Sociodemographics								
Age (years)				<0.001				0.004
35–42	10.3 (4.4)	510 (35.2)	34 (22.1)		8.2 (2.4)	514 (29.7)	10 (17.2)	
43–49	10.7 (4.1)	458 (31.6)	42 (27.3)		8.9 (2.7)	521 (30.1)	19 (32.8)	
50–57	11.5 (4.2)	342 (23.6)	48 (31.2)		9.5 (2.6)	502 (29.0)	13 (22.4)	
≥58	12.4 (4.2)	139 (9.6)	30 (19.4)		10.5 (3.8)	194 (11.2)	16 (27.6)	
Educational level				0.29				<0.001
Basic	10.3 (3.5)	202 (13.9)	58 (13.6)		9.2 (3.3)	309 (17.9)	17 (29.3)	
Apprenticeship	11.3 (5.4)	510 (35.2)	64 (41.6)		9.5 (3.1)	609 (35.2)	31 (53.4)	
High school/college	11.0 (4.1)	368 (25.4)	35 (22.7)		8.8 (2.5)	490 (28.3)	8 (13.8)	
University	10.8 (3.1)	369 (25.5)	34 (22.1)		8.3 (2.1)	323 (18.7)	2 (3.4)	
Marital status				0.28				<0.001
Married	10.9 (4.4)	951 (65.6)	97 (63.0)		8.7 (2.7)	882 (51.0)	14 (24.1)	
Others	11.2 (4.2)	498 (34.4)	57 (37.0)		9.4 (3.0)	849 (49.0)	44 (75.9)	
Health-related behaviours								
Smoking status				<0.001				0.06
Never	10.9 (3.7)	499 (34.4)	43 (27.9)		8.9 (3.1)	504 (29.1)	15 (25.9)	
Former	10.7 (3.8)	538 (37.1)	45 (29.2)		9.0 (2.6)	752 (43.4)	18 (31.0)	
Current	11.4 (5.5)	412 (28.5)	66 (42.9)		9.3 (3.0)	475 (27.5)	25 (43.1)	
Alcohol consumption				0.17				0.85
None	10.5 (6.1)	70 (4.8)	4 (2.6)		9.3 (3.1)	135 (7.8)	2 (3.4)	
Low	10.5 (3.6)	600 (41.4)	50 (32.5)		9.0 (2.9)	805 (46.5)	27 (46.6)	
Moderate	11.0 (3.4)	343 (23.7)	33 (21.4)		9.0 (2.5)	240 (13.9)	8 (13.8)	
High	11.8 (5.9)	279 (19.3)	50 (32.5)		9.5 (3.1)	101 (5.8)	8 (13.8)	
Missing	11.2 (4.3)	157 (10.8)	17 (11.0)		9.0 (2.8)	450 (26.0)	13 (22.4)	
Physical activity				0.01				0.36
None	11.1 (4.4)	451 (31.4)	63 (41.7)		9.2 (3.0)	526 (30.9)	23 (39.7)	
Once a week	10.9 (4.7)	191 (13.2)	17 (11.3)		8.6 (2.3)	140 (8.2)	1 (1.7)	
Twice a week	10.9 (4.2)	796 (55.4)	71 (47.0)		9.0 (2.8)	1039 (60.9)	34 (58.6)	
Biological risk factors								
Overweight/obese	11.1 (4.4)	842 (58.1)	104 (67.5)	0.02	9.3(3.1)	657 (38.0)	27 (47.4)	0.15
Total cholesterol ≥6.2 mmol/l	11.4 (4.3)	313 (22.4)	48 (31.8)	0.009	9.7 (2.7)	379 (22.5)	13 (22.4)	0.99
Triglycerides ≥2.2 mmol/l		249 (17.2)	41 (26.6)	0.004		98 (5.7)	1 (1.7)	0.20
Hypertension	11.8 (4.5)	460 (31.7)	82 (53.2)	0.001	9.9 (3.4)	387 (22.4)	24 (41.4)	<0.001
Diabetes	11.7 (5.2)	112 (7.7)	20 (13.0)	0.02	11.2 (3.8)	46 (2.7)	5 (8.6)	0.007
History of CVD	12.8 (7.2)	47 (3.2)	10 (6.5)	0.03	10.2 (2.7)	30 (1.7)	2 (3.4)	0.33
Albuminuria	13.2 (8.7)	62 (4.4)	22 (14.5)	<0.001	9.4 (2.7)	88 (5.1)	2 (3.6)	0.60
Medications/supplements use								
Diuretics	12.6 (6.2)	62 (4.3)	16 (10.4)	<0.001	10.7 (2.8)	74 (4.3)	9 (15.5)	0.001
Antidepressants	10.7 (3.1)	96 (6.6)	6 (3.9)	0.19	9.2 (2.7)	208 (12.0)	6 (10.3)	0.70
Vitamins	9.8 (3.1)	132 (9.1)	6 (3.9)	0.03	8.6 (2.4)	288 (16.6)	6 (10.3)	0.20

although this association only reached the level of statistical significance for remitted MDD. Among women, we did not observe significant associations between depression status and tHcy levels. The OR for both remitted and current MDD were even smaller than 1 (results not shown).

Second, results of analyses having divided tHcy levels into four categories are illustrated in Fig. 2. Among men, the fully adjusted OR for MDD tended to increase with tHcy levels but was statistically significant only at high tHcy level (≥ 15 μmol/L). In contrast, among women they tended to decrease with a borderline significant reduced OR at high tHcy level (Fig. 2).

Third, in the various age strata, as shown in Fig. 3, all fully adjusted OR estimating the associations between high tHcy and MDD were largely above 1 among men. The association between tHcy and MDD, however, was stronger and statistically significant only among older men (aged ≥ 58 y).

Table 2 Baseline characteristics of participants as a function of lifetime major depressive disorder (MDD) by sex.

	Men			Women		
	MDD			MDD		
	No	Yes	*p* value	No	Yes	*p* value
Number (%)	1098 (68.5)	505 (31.5)		825 (46.1)	964 (53.9)	
Sociodemographics						
Age (years)			0.001			0.01
35–42	351 (32.0)	193 (38.2)		217 (26.3)	307 (31.8)	
43–49	348 (31.7)	152 (30.1)		241 (29.2)	299 (31.0)	
50–57	277 (25.2)	113 (22.4)		256 (31.0)	259 (26.9)	
≥58	122 (11.1)	47 (9.3)		111 (11.5)	99 (10.3)	
Educational level			0.009			0.23
Basic	160 (14.5)	63 (12.4)		160 (19.4)	166 (17.2)	
Apprenticeship	404 (36.8)	170 (33.7)		295 (35.8)	345 (35.8)	
High school/college	282 (25.7)	121 (24.0)		226 (27.4)	272 (28.2)	
University	252 (23.0)	151 (29.9)		144 (17.5)	181 (18.8)	
Marital status			<0.001			<0.001
Married	758 (69.0)	290 (57.4)		476 (57.7)	420 (43.6)	
Others	340 (31.0)	215 (42.6)		349 (42.3)	544 (56.4)	
Health-related behaviours						
Smoking status			0.03			0.02
Never	394 (35.9)	148 (29.3)		384 (46.5)	386 (40.0)	
Former	404 (36.8)	179 (35.4)		243 (29.5)	276 (28.6)	
Current	300 (27.3)	178 (35.3)		198 (24.0)	302 (31.4)	
Alcohol intake			0.20			0.81
No	56 (5.1)	18 (3.5)		63 (7.6)	74 (7.7)	
Low	440 (40.1)	210 (41.6)		369 (44.8)	463 (48.0)	
Moderate	267 (24.3)	109 (21.6)		130 (15.8)	118 (12.3)	
High	223 (20.3)	106 (21.0)		49 (5.9)	60 (6.2)	
Missing	112 (10.2)	62 (12.3)		214 (25.9)	249 (25.8)	
Physical activity			0.24			0.04
None	360 (33.1)	154 (30.8)		237 (29.1)	312 (32.9)	
Once a week	147 (13.5)	61 (12.2)		59 (7.2)	82 (8.6)	
Twice a week	582 (53.4)	285 (57.0)		518 (63.6)	555 (58.5)	
Biological risk factors						
Overweight/obese	670 (61.0)	276 (54.8)	0.01	322 (39.1)	362 (37.7)	0.53
Total cholesterol ≥ 6.2 mmol/l	250(23.5)	111 (22.8)	0.75	184 (22.9)	208 (22.1)	0.67
Triglycerides ≥ 2.2 mmol/l	187 (17.0)	103 (20.4)	0.10	52 (6.3)	47 (4.9)	0.19
Hypertension	387 (35.2)	155 (30.7)	0.07	196 (23.8)	215 (22.3)	0.47
Diabetes	91 (8.3)	41 (8.1)	0.91	21 (2.5)	30 (3.1)	0.47
History of CVD	36 (3.3)	21 (4.2)	0.38	14 (1.7)	18 (1.9)	0.79
Albuminuria	56 (5.3)	28 (5.6)	0.75	39 (4.8)	51 (5.4)	0.57
Medication/supplement use						
Diuretics	50 (4.6)	28 (5.5)	0.12	43 (5.2)	40 (4.1)	0.68
Antidepressants	31 (2.8)	71 (14.1)	<0.001	45 (5.5)	169 (17.5)	<0.001
Vitamins	81 (7.4)	57(11.3)	0.01	137 (16.6)	157 (16.3)	0.86

4. Discussion

The main finding of this population-based study is that elevated serum tHcy concentrations were associated with greater odds of meeting the diagnostic criteria for lifetime MDD among men, independently of sociodemographic characteristics, health-related behaviours, biological risk factors and medication/vitamins use. This was the case for both remitted and current MDD, even though the association was more evident for remitted MDD. For this association, we observed a threshold effect at levels ≥15 μmol/L, in line with what has been previously reported for the associations between tHcy concentrations and depressive symptoms (Bjelland et al., 2003), as well as cardiovascular and non-cardiovascular mortality (Vollset et al., 2001). Among women, there was no significant association between tHcy levels and MDD and the association even tended to be in the opposite direction.

4.1. Findings in the context of previous studies

To the best of our knowledge, this is the largest population-based study examining the association of tHcy levels with MDD according to DSM-IV. In contrast to previous studies that

Table 3 Association between high total homocysteine (tHcy $\geq$ 15 μmol/L) and lifetime major depression disorder (MDD) in men and women.

	Major depressive disorder			
	Men		Women	
	n events/*n* total	OR 95% CI	*n* events/*n* total	OR 95% CI
Model 1				
tHcy $<$ 15 μmol/L	445/1449	1	936/1731	1
tHcy $\geq$ 15 μmol/L	60/154	1.52 (1.07–2.16)*	28/58	0.71 (0.41–1.22)
Model 2				
tHcy $<$ 15 μmol/L	440/1438	1	921/1705	1
tHcy $\geq$ 15 μmol/L	60/151	1.56 (1.09–2.21)*	28/58	0.70 (0.41–1.21)
Model 3				
tHcy $<$ 15 μmol/L	419/1359	1	902/1668	1
tHcy $\geq$ 15 μmol/L	58/149	1.47 (1.02–2.12)*	25/55	0.60 (0.34–1.05)
Model 4				
tHcy $<$ 15 μmol/L	445/1449	1	936/1731	1
tHcy $\geq$ 15 μmol/L	60/154	1.67 (1.17–2.39)**	28/58	0.74 (0.42–1.28)
Model 5				
tHcy $<$ 15 μmol/L	414/1348	1	888/1644	1
tHcy $\geq$ 15 μmol/L	58/146	1.71 (1.18–2.50)**	25/55	0.61 (0.34–1.08)

Model 1: ORs adjusted for age, educational level and marital status.
Model 2: Model 1 additionally adjusted for smoking and physical activity.
Model 3: Model 1 additionally adjusted for overweight/obesity status, total cholesterol, triglycerides, history of CVD, hypertension, diabetes, and albuminuria.
Model 4: Model 1 additionally adjusted for antidepressants, diuretics and vitamins use.
Model 5: ORs adjusted for all aforementioned.
* $p < 0.05$.
** $p < 0.01$.

used depressive symptoms rather than the algorithmically defined diagnosis of depression as the variable of interest (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; Loprinzi and Cardinal, 2012), misclassification of MDD cases was minimized in our study. The high prevalence of MDD was most likely attributable to the low threshold to enter the depression section in our DIGS version. As we intended to also assess algorithmically defined depressive syndromes below the DSM-IV threshold, the one-week duration specification of the original DIGS in the screening questions for depression was removed. Accordingly, the large majority of the participants entered the section. We are aware of only four previous studies that have examined the association of tHcy with MDD according to DSM-III or IV (Bottiglieri et al., 2000; Morris et al., 2003; Tiemeier et al., 2002; Pascoe et al., 2012).

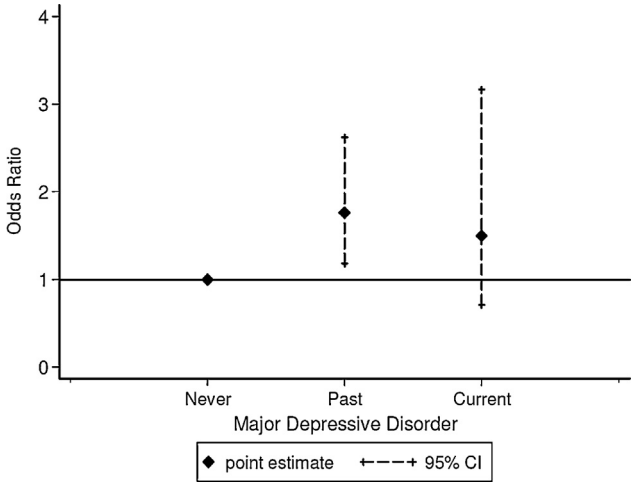

Figure 1 Elevated total homocysteine (tHcy) levels (serum concentration $\geq$ 15 μmol/L, as the independent variable of interest) and risk of past (remitted) and current major depressive disorder (MDD) in men (as the three-category dependent variable). ORs adjusted for age, educational level, marital status, smoking, physical activity, overweight/obesity status, total cholesterol, triglycerides, history of CVD, hypertension, diabetes, albuminuria, antidepressants, diuretics and vitamins use.

Our study has several strengths that helped overcome the limitations of the four previous studies (Bottiglieri et al., 2000; Tiemeier et al., 2002; Morris et al., 2003; Pascoe et al., 2012) that assessed depressive disorders as well as those that only evaluated depressive symptoms using depression scales (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). In our study, we were able to control for a wide range of potentially confounding and/or mediating variables and to conduct several additional analyses. Moreover, our sample was recruited from the general population and was not restricted to older or younger age ranges.

Although, we did not find a statistically significant interaction between tHcy and sex in relation to MDD, our results suggest that the association of tHcy with depression differs by sex with a significant positive association in men and no

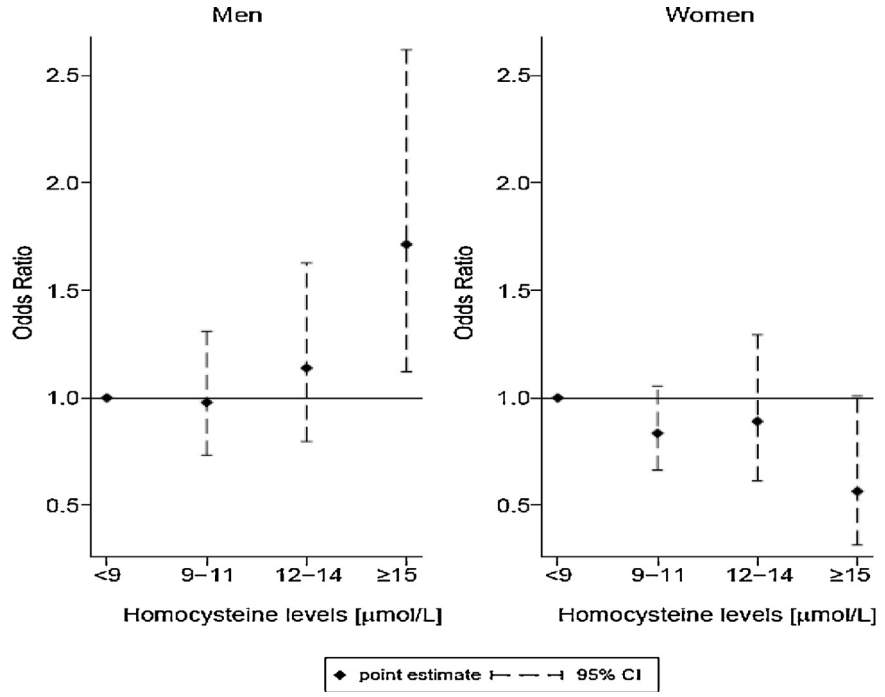

Figure 2 Total homocysteine (tHcy, as the independent variable of interest) levels and risk of lifetime major depressive disorder (MDD, as the dependent variable) in men and women. ORs adjusted for age, educational level, marital status, smoking, physical activity, overweight/obesity status, total cholesterol, triglycerides, history of CVD, hypertension, diabetes, albuminuria, antidepressants, diuretics and vitamins use.

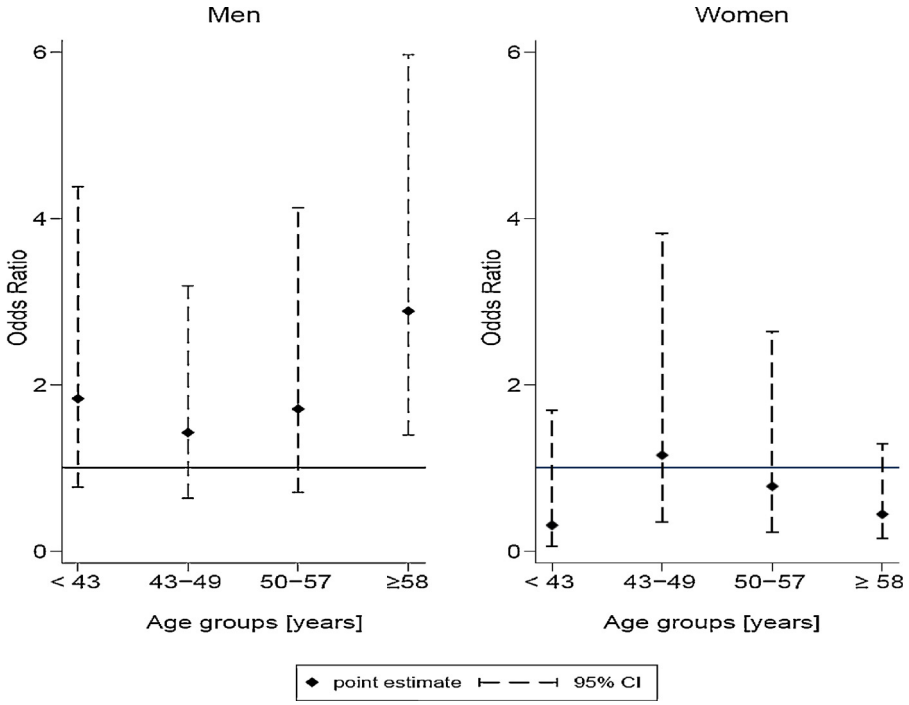

Figure 3 Elevated total homocysteine (tHcy) levels (serum concentration $\geq$ 15 μmol/L, as the independent variable of interest) and risk of lifetime major depressive disorder (MDD, as the dependent variable) in men and women by age groups. ORs adjusted for age, educational level, marital status, smoking, physical activity, overweight/obesity status, total cholesterol, triglycerides, history of CVD, hypertension, diabetes, albuminuria, antidepressants, diuretics and vitamins use.

association, or even a tendency towards a negative association, in women. One reason could be that the distribution of tHcy strongly differed by sex. Indeed, tHcy concentrations ranged from 3.2 to 39.7 μmol/L in women, whereas these concentrations ranged from 4.5 to 67.1 μmol/L in men. As a consequence the prevalence of elevated tHcy among women (concentration of 15 μmol/L or more) was estimated at 3.2%, which was 3 times lower than that of men. Furthermore, there was less variability in the distribution of tHcy levels among women as indicated by smaller variance (8.11 vs. 18.9 for men) and SD (2.8 vs. 4.4 for men) values. Another reason of the observed effect modification of sex on the association of tHcy with MDD could be due, at least in part, to the effect of sex hormones. In women, tHcy levels are lower before than after menopause (Wouters et al., 1995; Hak et al., 2000). Furthermore, hormone-replacement therapy (HRT) used in post-menopausal women was found to substantially reduce tHcy levels (Walsh et al., 2000; Gol et al., 2006). Although data on current HRT use were not available, the results of our sensitivity analyses as illustrated in Fig. 3 did not support this latter possibility. Therefore, further studies have to address the issue of differential associations between tHcy levels and MDD by sex.

Results from post hoc analyses also showed that men with elevated tHcy levels had higher odds of meeting the diagnostic criteria for both remitted and current MDD, even if it was to a lesser extent for current MDD. Only 17.8% (n = 90) of the 505 men with a lifetime MDD were depressed (current MDD) at the psychiatric evaluation. The lack of statistical significance might have been due to the lower statistical power; an indication of this possibility being a wider confidence interval observed for the association between tHcy and current MDD in Fig. 1. Nonetheless, this finding is consistent with prior data from the Health in Men Study conducted among a community sample of 3752 men aged 70 or older (Almeida et al., 2008). The results of this study showed that tHcy is associated with both current depression and a history of depression assessed based on the Geriatric Depression Scale and self-reported past or current treatment for depression.

The nature of the relationship between tHcy and depression is still unclear. The fact that tHcy remained significantly elevated in men with past MDD episode represents an important finding that may help reconcile inconsistent findings and advance our understanding of the tHcy—depression relationship. This would mean that the raised tHcy could be a consequence of depression, even if we cannot rule out that the possibility that elevated tHcy causes depression. The relationship between tHcy and depression could be bidirectional or attributable to shared pathogenic factors such as genes or lifestyle that could favour both elevated tHcy levels and depression. However, lifestyle could also be an intermediate factor within the potentially bidirectional relationship between tHcy and depression. Indeed, there is some evidence from previous research showing that people with a history of depressive symptoms or diagnosed depression are likely to exhibit poor health behaviours (Breslau et al., 1993; Whooley et al., 2008), which entail an increased risk factors for elevated tHcy levels (Refsum et al., 2006). However, although elevated tHcy levels and MDD were found to be associated with physical inactivity and/or smoking in our study, the association between tHcy and MDD remained significant after adjustment for these variables. It should be noted that we were not able to take into account the trajectories of health-related behaviours over time, which can be influenced by the course of depression. In addition, we only took into account physical inactivity at the time of the interview and did not assess other relevant behaviours such as diet. For this reason we could not determine the potential role of nutritional deficiencies related to appetite loss in depression, which have been found to be associated with raised tHcy levels and folate deficiency (Bottiglieri et al., 2000; Tiemeier et al., 2002).

Conversely, elevated tHcy have been found to be associated with several chronic medical conditions such as CVD (Welch and Loscalzo, 1998) and diabetes (Targher et al., 2000) which in turn could predispose to depressive disorders or symptoms (Lichtman et al., 2008; Pan et al., 2010). However, this explanation was not supported by our data. Indeed although medical conditions including CVD, diabetes, hypertension, albuminuria were associated with elevated tHcy levels, but they were not associated with MDD.

4.2. Limitations

The present findings should be interpreted in the light of several limitations. First, in spite of its size, this urban population-based sample is probably much healthier than the sample of previous studies composed of elderly people. As a consequence, the prevalence of elevated tHcy level was low, particularly among women, which decreased the statistical power to detect associations with tHcy. Secondly, the cross-sectional design of our study limits our ability to investigate the nature (direction of causality) of the association between tHcy and depression. Thirdly, although we have adjusted for a wide range of covariates, there could be residual confounding or unconsidered risk factors such as dietary patterns, specific vitamin status and genetics factors (Bjelland et al., 2003; Refsum et al., 2006) that may contribute to the relation between tHcy and depression. Finally, our study was conducted among men and women with Caucasian origin, which limits the generalization of our findings

4.3. Conclusions

In conclusion, the results of this large population-based study suggest that elevated serum tHcy concentrations were associated with increased odds of meeting criteria for a diagnosis of lifetime MDD and remitted MDD in men, but not in women. The fact that tHcy concentrations were elevated in men who met the criteria for a remitted MDD lends support to the hypothesis that depressive episodes lead to durably increased tHcy levels which could explain, at least partially, the observed links between depression, fatal and non-fatal CVD events. Further studies are needed to test these mechanisms and to explore whether lowering serum homocysteine levels in depressed patients reduces adverse CVD outcomes.

Role of the funding source

The funding source had no role in the design and conduct of the study; in the collection, management, analysis, and

interpretation of the data; or in the preparation, review, or approval of the manuscript.

Conflict of interest

None declared.

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