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Mood disorders and circulating levels of inflammatory markers in a longitudinal population-based study

Running title: Mood disorders and inflammatory markers

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ABSTRACT

Background: There has been increasing evidence that chronic low-grade inflammation is associated with mood disorders. However, the findings have been inconsistent because of heterogeneity across studies and methodological limitations. Our aim is to prospectively evaluate the bi-directional associations between inflammatory markers including Interleukin (IL)-6, Tumor Necrosis Factor (TNF)-α and high sensitivity C-reactive protein (hsCRP) with mood disorders.

Methods: The sample consisted of 3,118 participants (53.7% women; mean age: 51.0, s.d. 8.8 years), randomly selected from the general population, who underwent comprehensive somatic and psychiatric evaluations at baseline and follow-up (mean follow-up duration = 5.5 years, s.d. 0.6). Current and remitted mood disorders including bipolar and major depressive disorders (MDD) and its subtypes (atypical, melancholic, combined atypical and melancholic, and unspecified) were based on semi-structured diagnostic interviews. Inflammatory biomarkers were analyzed in fasting blood samples. Associations were tested by multiple linear and logistic regression models.

Results: Current combined MDD (β=0.29, 95% CI: 0.03-0.55) and current atypical MDD (β=0.32, 95% CI: 0.10-0.55) at baseline were associated with increased levels of hsCRP at follow-up. There was little evidence for inflammation markers at baseline predicting mood disorders at follow-up.

Conclusions: The prospective unidirectional association between current MDD subtype with atypical features and hsCRP levels at follow-up suggests that inflammation may be a consequence of this condition. The role of inflammation, particularly hsCRP that is critically involved in cardiovascular diseases, warrants further study. Future studies may examine whether treatment of depression may lead to a decrease in inflammation and consequently a decrease in cardiovascular risk.

Key-words: mood disorders; atypical depression; pro-inflammatory cytokines; C-Reactive protein; prospective study; cardiovascular risk factors.

INTRODUCTION

Mood disorders and cardiovascular diseases (CVD) are among the highest sources of morbidity and premature mortality worldwide (GBD 2015 DALYs and HALE Collaborators 2016) . Moreover, their high comorbidity (Van der Kooy *et al.* 2007, Glaus *et al.* 2013) is associated with even greater disability adjusted life years than either disorder alone (Charlson *et al.* 2013). An increasingly recognized mechanism to explain comorbidity of CVD with mood disorders is common underlying low-grade inflammation. Specifically, there is a consistent association between circulating levels of pro-inflammatory cytokines, such as Interleukin (IL)-1β, IL-6 and Tumor Necrosis Factor (TNF)-α, and the acute phase reactant C-Reactive Protein (CRP) with both mood disorders(Howren *et al.* 2009, Dowlati *et al.* 2010, Modabbernia *et al.* 2013, Glaus *et al.* 2014) and CVD (Baune *et al.* 2012). Alternatively, such inflammatory processes could also provoke mood disorders or CVD through, for instance, stress-induced perturbation of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Rosmond *et al.* 2000, Watson 2006). Conversely, mood disorders could induce inflammation through similar mechanisms (Rosenblat *et al.* 2014).

Although the bulk of prospective research on inflammatory markers and CVD has focused on major depression, comparably few studies have examined the extent to which associations extend to other mood disorders, such as bipolar disorder (BPD)(Van der Kooy *et al.* 2007, Modabbernia *et al.* 2013). In a recent meta-analysis of 25 cross-sectional studies and 2 longitudinal analyses (changes in CRP levels before and after treatment for mania and depression), BPD disorder was associated with increased levels of CRP (Fernandes *et al.* 2016). In another meta-analysis of 30 cross-sectional studies, BPD disorder was associated with increased levels of IL-6 and TNF-α (Modabbernia *et al.* 2013). Moreover, few longitudinal studies have examined depressive subtypes (Rothermundt *et al.* 2001, Kaestner *et al.* 2005, Yoon *et al.* 2012, Lamers *et al.* 2013, Glaus *et al.* 2014, Hickman *et al.* 2014, Rudolf *et al.* 2014) that have been shown to be highly heterogeneous (Schmidt *et al.* 2011, Lopresti *et al.* 2014)

and even fewer studies have considered the well-established comorbidity among mental disorders (Stewart *et al.* 2009, Kivimaki *et al.* 2014) or current versus past disorders (Whooley *et al.* 2008).

With respect to directionality, longitudinal studies of the links between mood disorders and inflammation have predominantly been performed in patients with a major depressive disorder (MDD) (Valkanova *et al.* 2013, Chocano-Bedoya *et al.* 2014, Kivimaki *et al.* 2014, Tully *et al.* 2015). Recent meta-analyses (Valkanova *et al.* 2013) and more recent studies (Chocano-Bedoya *et al.* 2014, Tully *et al.* 2015) have shown that these associations between inflammatory factors and mood disorders may be partially attributable to potential confounders, including body mass index (BMI) and smoking. Similar findings regarding mediation by BMI and behavioral cardiovascular risk factors (CVRFs) have also emerged from prospective studies of inflammation as a potential consequence of mood disorders (Matthews *et al.* 2007, Gimeno *et al.* 2009, Stewart *et al.* 2009, Duivis *et al.* 2011). However, to date, the few studies that have examined the bi-directional associations simultaneously have yielded conflicting results (Gimeno *et al.* 2009, Stewart *et al.* 2009, Matthews *et al.* 2010, Duivis *et al.* 2011). The aggregate findings from these studies highlight the importance of incorporating CVRFs including diabetes (Marques-Vidal *et al.* 2012a), overweight (Marques-Vidal *et al.* 2012b, Kiecolt-Glaser *et al.* 2015), smoking (Yanbaeva *et al.* 2007), chronic alcohol consumption (Achur *et al.* 2010) and physical inactivity (Hamer 2007, Kiecolt-Glaser *et al.* 2015) along with depression and anxiety (e.g. (Agosti *et al.* 2006, Mezuk *et al.* 2008, Chaiton *et al.* 2009, Anthenelli 2010, Luppino *et al.* 2010, Glaus *et al.* 2013, Lasserre *et al.* 2014, Kiecolt-Glaser *et al.* 2015)), when examining the association with inflammation.

Our previous cross-sectional findings from a large community cohort revealed that there were significantly elevated levels of high sensitivity CRP (hsCRP) among those with the atypical subtype of depression and bipolar disorders, but these associations were explained by concurrent CVRFs, such as BMI, diabetes and hypertension (Glaus *et al.* 2014). In the present study, we extend these earlier cross-

sectional analyses from our large community-based cohort in Lausanne, Switzerland, to examine the directionality, specificity, timing, and potential causal versus common etiologic mechanisms for associations between mood disorders and markers of a chronic low-grade inflammation by addressing the following aims: (1) to evaluate the 5-year prospective associations between mood disorders including their subtypes, and changes in circulating levels of specific inflammatory markers (IL-6, TNF-α, hsCRP) to determine the specificity of the associations; (2) to assess the directionality of links between inflammatory markers and mood disorders; (3) to examine whether the markers comprise state versus trait indices by comparing remitted versus current disorders, as well as incident cases; and (4) to examine the role of health behaviors, CVRFs, and treatment factors that may influence this association. Based on our previous cross-sectional study (Glaus *et al.* 2014), we hypothesized to find an association between the atypical subtype of depression and increased levels of inflammatory markers, whereas other subtypes of major depressive disorders were not expected to be associated with increased inflammation.

METHODS AND MATERIALS

Study sample

We drew the data for the present investigation from CoLaus|PsyCoLaus (Firmann *et al.* 2008, Preisig *et al.* 2009), a cohort study designed to prospectively assess the associations between mental disorders and CVD or CVRFs in the community. The sample was randomly selected from the civil register of the city of Lausanne (Switzerland) in 2003. Sixty-seven percent of participants between 35 and 66 years-of age (n=5,535), who underwent the physical exam between 2003 and 2006, also accepted the psychiatric evaluation, resulting in a sample of 3,719 individuals at baseline (Preisig *et al.* 2009) (see Figure 1, flow chart). The mean interval between the physical and psychiatric evaluations at baseline was 1.33 years (s.d. 0.51). Five years later, 3,191 participated in the physical exam (85.8% participation). Among them,

61 participants were excluded due to missing information on inflammatory markers both at baseline and follow-up, 9 subjects were excluded due to missing information on mental disorders and 3 subjects were excluded due to missing information on CVRFs. The final sample used to examine associations between mood disorders at baseline and inflammation at follow-up consisted of 3,118 participants in total (53.7% women; mean age: 51.0, s.d. 8.8 years): 2,796 participants were analyzed for cytokines levels, and 2,896 for hsCRP levels. The mean follow-up duration for the physical examination was 5.5 years (s.d. 0.6 years). The mean follow-up duration for the mental health assessment was 5.5 years (s.d. 0.8). The number of participants with data on the psychiatric evaluation at follow-up was 2,840. Among them, 258 participants were excluded due to missing information on inflammatory markers and 2 participants due to missing information on CVRFs. The resulting number of participants used to determine the association between inflammation at baseline and mental disorders at follow-up was 2,580. The Institutional Ethics' Committee of the University of Lausanne approved the CoLaus and the PsyCoLaus study. All participants provided written informed consent for the study protocol.

Measurements

Mood disorders and comorbid disorders

Mental disorders at baseline and follow-up were assessed using the French version (Leboyer *et al.* 1995) of the semi-structured Diagnostic Interview for Genetic Studies (DIGS), which was developed and validated by the National Institute of Mental Health (Nurnberger *et al.* 1994). The French version of this instrument revealed adequate inter-rater and test-retest reliability for major mood (Preisig *et al.* 1999) and substance use disorders (Berney *et al.* 2002). The DIGS was completed with sections on generalized anxiety and phobia disorders using questions from the Schedule for Affective Disorders and Schizophrenia-Lifetime and Anxiety disorder version (SADS-LA (Endicott *et al.* 1978)), which also revealed satisfactory test-retest reliability (Leboyer *et al.* 1991, Rougemont-Buecking *et al.* 2008). Interviewers were required to be masters-level psychologists and were trained over a two-month

period. In order to provide ongoing supervision throughout the study, each interview and diagnostic assignment was reviewed by an experienced senior psychologist. Diagnoses were assigned according to the DSM-IV. Following Angst et al. (Angst *et al.* 2006), MDD was subtyped into: 1) MDD with at least one atypical and one melancholic episode or MDD with atypical and melancholic features simultaneously (combined type); 2) MDD with at least one atypical (but no melancholic) episode; 3) MDD with at least one melancholic (but no atypical) episode; and 4) MDD with neither atypical nor melancholic episodes (unspecified type). We defined MDD as current if it was present at the time of the physical evaluation.

Inflammatory markers

HsCRP was assessed during baseline and follow-up physical evaluations using immunoassay and latex HS (IMMULITE 1000-High, Diagnostic Products Corporation, LA, CA, USA), with maximum intra- and interbatch coefficients of variation of 1.3% and 4.6%, respectively (Firmann *et al.* 2008). Subjects with a hsCRP level higher than 10 mg/l were excluded as such an elevation is likely to be attributable to acute infection (Pearson *et al.* 2003). For the baseline and follow-up cytokine measurements, serum was preferred to plasma, as it has been shown that different anticoagulants may differentially affect absolute cytokine levels (Skeppholm *et al.* 2008). Serum samples were stored at -80°C before assessment and sent on dry ice to the laboratory. As previously described, cytokine levels were measured using a multiplexed particle-based flow cytometric cytokine assay (Marques-Vidal *et al.* 2011). Lower detection limits (LOD) for IL-6 and TNF-α were 0.2 pg/ml. Good agreement between signal and cytokine was found within the assay range ($R^2 \geq 0.99$).

Covariates

Data were collected on age, race (Caucasian versus non-Caucasian), marital status (living alone versus living with someone) and health-related behaviors at baseline including smoking (never, former, current) and physical inactivity (no or low versus at least 20 minutes twice a week). Information on

socio-economic status (SES) and on psychotropic drug treatment was derived from the DIGS. The level of SES was assessed using the Hollingshead scale (Hollingshead 1975). The section on psychotropic drug treatment covered all types of antidepressants, mood stabilizers (lithium and anti-epileptics) and antipsychotics. Moreover, information on aspirin and statin use was collected during the baseline physical evaluation (never versus occasional versus regular use). The following biological variables were measured during the baseline physical evaluation: BMI (weight in kilograms divided by height in meters squared), diabetes (fasting blood glucose ≥ 7 mmol/l or treatment for diabetes), dyslipidemia (HDL-cholesterol < 1 mmol/l, or LDL-cholesterol ≥ 4.1 mmol/l, or triglycerides ≥ 2.2 mmol/l, or treatment with a lipid-lowering drug), hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or treatment for hypertension).

Statistical analysis

Statistical analyses were conducted using the Statistical Analysis System (SAS Institute Inc., Cary, NC, USA), version 9.3 for Windows. Age was standardized. Descriptive data for demographic characteristics, comorbid disorders, medication, health-related behaviors, physical risk factors for CVD and inflammatory marker levels were derived by lifetime mood disorders and Chi-square and Kruskal-Wallis tests were used to determine the difference between mood disorders. P-values were not adjusted for multiple testing because the hypothesized associations between mood disorders and inflammatory markers were specified a priori.

Associations between current and remitted mood disorders at baseline and changes in inflammatory markers at follow-up were determined using multiple linear regression models. Box-Cox transformation was applied to the response variable whenever a deviation from fundamental assumptions was observed. Values below the LOD of 0.2 [pg/ml] (i.e., 5% of values for IL-6, 0.5% of values for TNF-α) were considered as censored observations. IL-6 and TNF-α were analyzed with the qualitative and limited

dependent variable model (QLIM) with the threshold of -1.65 [log (pg/ml)] as the meaningful lower bound of observed values.

A multiple linear regression model was performed on naturally log-transformed and standardized observed values. Three models of increasing complexity were computed. Model 1 included one single mood disorder (current and remitted) at a time as the independent variable, adjusted for the corresponding inflammatory marker at baseline. Model 2 included current and remitted mood disorders simultaneously in order to determine the associations of specific mood disorder with inflammatory markers at follow-up, adjusting for the length of follow-up, sociodemographic characteristics (sex, age, SES, race and marital status), comorbid disorders (anxiety and substance use disorders), health-related behaviors and physical risk factors for CVD at baseline and the covariate of Model 1. In case of significant associations, additional models also adjusted for the occurrence of new episodes in order to test whether the associations persist after the offset of depressive episodes. Similar models adjusted for the occurrence of new physical risk factors for CVD during the follow-up in order to test whether the prospective associations between mood disorders and inflammation marker levels were independent of the occurrence of these new risk factors.

Associations between inflammatory markers at baseline and a history of mood disorders during the follow-up period were determined using logistic regression models. Two models were computed. Model 1 included all inflammatory markers simultaneously, adjusting for the corresponding history of mood disorder at baseline. Model 2 was further adjusted for the length of follow-up, sociodemographic characteristics, health-related behaviors and physical risk factors for CVD.

RESULTS

Sample characteristics

The description of the cohort of 3,118 participants used for the assessment of the prospective associations between mood disorders at baseline and the concentrations of inflammatory markers at follow-up is presented in Table 1. The groups (bipolar disorder, MDD subtypes and no history of mood disorders) differed with respect to sex, age, marital status, comorbid disorders, medication, current smoking status, BMI and hypertension. Moreover, the groups also differed with respect to hsCRP levels at baseline and at follow-up.

Associations between mood disorders at baseline and inflammatory markers at follow-up

Associations between current and remitted mood disorders at baseline and changes in levels of inflammatory markers are presented in Table 2 and 3. When models were only adjusted for the corresponding inflammatory marker at baseline (Table 2), current MDD, as well as the current combined and atypical MDD subtypes were associated with increased hsCRP levels. Moreover, current combined MDD was associated with decreased IL-6 levels. No significant associations were found for remitted mood disorders with inflammatory markers. When the model was further adjusted for potential confounders, MDD was no longer significantly associated with hsCRP levels (β=0.09, 95%CI -0.02-0.21). In contrast, current combined MDD was associated with increased hsCRP levels and decreased IL-6 levels and current atypical MDD was associated with increased hsCRP levels at follow-up (Table 3). Moreover, remitted melancholic MDD was associated with decreased IL-6 levels at follow-up in the fully adjusted model (Table 3).Additional analyses revealed that the occurrence of new mood episodes during the follow-up did not affect the size of the associations between current mood disorders at baseline and the hsCRP at follow-up. Similarly, the occurrence of incident physical risk factors for CVD did not account for the associations between current combined MDD or current atypical MDD at baseline and the hsCRP at follow-up.

Since an association was found between the atypical MDD subtype and increased hsCRP levels at follow-up, we also looked at the correlation between the age of onset of atypical MDD and inflammatory

markers. Interestingly, later atypical MDD onset was correlated with increased hsCRP levels (Pearson correlation = 0.16, p-value = 0.0214).

Associations between inflammatory markers at baseline and mood disorders at follow-up

Regarding the associations between inflammatory markers at baseline and mood disorders at follow-up, higher levels of TNF-α were associated with a decreased risk of MDD and of the MDD atypical and unspecified subtypes after controlling for a history of depression at baseline (Table 4). After controlling for all the covariates (Model 2), higher levels of TNF-α were still associated with a decreased risk of MDD and of the MDD unspecified subtype, but not with the MDD atypical subtype. Moreover, levels of IL-6 and hsCRP at baseline were not associated with any mood disorders at follow-up.

We also tested the associations between inflammatory markers at baseline and incident cases of mood disorders excluding subjects that already had a lifetime history of this disorder at baseline. However, no significant associations were found (results not shown).

DISCUSSION

The present study prospectively assessed the bi-directional 5-year associations between mood disorder and its subtypes with several inflammatory markers with serial adjustments for sociodemographic, comorbid mental disorders, medication use, health behaviors, and CVRFs, in a large community sample of adults. Our results showed differential associations depending on temporal ordering, current versus remitted status of the mood disorder, the specific type of mood disorder and different indices of inflammation. The major finding is that there is an association between the current atypical subtype of MDD at baseline with increased levels of hsCRP at follow up, whereas inflammatory levels at baseline were not associated with subsequent atypical MDD at follow-up. This unidirectional association indicates that this disorder may be causally related to increased inflammation, rather than inflammation

comprising a vulnerability factor for mood disorders. Future studies with more closely timed follow-up assessments may inform potential mechanisms for elevation of hsCRP among those with this condition. Our finding of unidirectional associations between MDD and elevated hsCRP levels appear to be specific to the atypical subtype of MDD, which is characterized by somatic symptoms including sleep, energy and eating behavior (Rothermundt *et al.* 2001, Kaestner *et al.* 2005, Stewart *et al.* 2009, Duivis *et al.* 2011, Copeland *et al.* 2012, Lamers *et al.* 2013, Glaus *et al.* 2014, Hickman *et al.* 2014, Rudolf *et al.* 2014, Schmidt *et al.* 2014). This finding suggests that the atypical MDD is associated with more detectable immune dysfunction. This could be a primary characteristic of this disorder or reflect other indirect factors, such as greater disturbance of circadian systems, HPA systems or other relevant immune modulators. A similar link between cumulative depressive episodes and CRP at follow-up in a prospective study of a community sample of youth would confirm this explanation and further imply that the associations observed herein may be present across the life span (Copeland *et al.* 2012).The specificity of the findings with respect to the atypical subtype rather than BPD (Modabbernia *et al.* 2013), as shown in previous studies of adults and youth, further suggests that the somatic manifestations of depression may be etiologically related to inflammation. Although our sample of subjects with a lifetime history of BPD only included 55 subjects, which does not allow us to draw definitive conclusions, our results do not provide any clues for increased levels of inflammation in these subjects, which could also be attributable to the fact that except for two all these bipolar subjects were in remission. Interestingly, a previous case-control study (Cunha *et al.* 2008) evaluating BPD patients in different phases of the illness found increased hsCRP levels in patients with a current manic episode compared to depressed, euthymic patients and healthy controls suggesting a state-dependent effect of manic episodes. Moreover, recent studies also found that mania and to a lesser extent depression in BPD patients are associated with pro-inflammatory cytokines (Muneer 2016). To our knowledge, no studies have examined depressive subtypes in BPD compared to MDD patients and healthy controls.

Future prospective studies should further investigate the different state-related associations between mood disorder subtypes and inflammation.

The lack of association between inflammatory markers at baseline and subsequent mood disorders at follow-up suggests that inflammation may not be a risk factor for the onset of mood disorders. This result extends the findings of two previous longitudinal studies, which found that depression predicted higher inflammation, whereas inflammation did not predict depression (Stewart *et al.* 2009, Duivis *et al.* 2011). However, our results are in contradiction with two studies that showed inflammatory levels to predict depressive symptoms, but depressive symptoms did not predict changes in inflammation levels (Gimeno *et al.* 2009, Matthews *et al.* 2010). Moreover, our findings are also in contradiction with a previous meta-analysis (Valkanova *et al.* 2013) and another prospective study which found increased CRP levels to be associated with increased depressive symptoms (Tully *et al.* 2015). These discrepancies could be due to methodological differences. Indeed, depressive symptoms and not depression diagnosis were assessed and no depressive subtypes were analyzed.

The restriction of our findings to the hsCRP, which has been shown to lead to broader manifestations of the metabolic syndrome, rather than the pro-inflammatory cytokines, particularly among those with current disorders rather than symptoms alone (Gimeno *et al.* 2009, Matthews *et al.* 2010), further suggests that the physical symptoms of these conditions may induce a stress-like physiologic reaction in affected individuals. Accordingly, depression may contribute to a chronic low-grade inflammatory state, which, in turn, might lead to a vascular pathology and ultimately to atherosclerotic vascular disease (Wagner *et al.* 2015). Several potential pathophysiological mechanisms have been suggested to underlie the association between depression and higher inflammation, including HPA axis activation and oxidative stress (Rosenblat *et al.* 2014). However, future longitudinal studies are needed to confirm these potential mechanisms.

Our results should be interpreted in the context of several limitations. First, there was an interval of almost one year between the physical and the psychiatric evaluations. Although the timing of depressive episodes was elicited in our diagnostic interviews, we cannot exclude misclassification regarding the "current" status of disorders at the time of the physical evaluation. Second, inflammatory markers were only assessed once at baseline and 5.5 years later at follow-up, which only partially reflected the dynamic temporal relationship between mood disorders and inflammatory markers over time. However, despite this limitation our findings still support longstanding increase of inflammation in subjects with specific subtypes of mood disorders. Third, low-grade inflammation was measured by hsCRP and 2 pro-inflammatory cytokine levels, but other pro-inflammatory (i.e. IL-1β, IL-2, IFN-γ) or anti-inflammatory (i.e. IL-4, IL-8, IL-10) cytokines and other potential biomarkers of inflammation, such as cortisol, leucocytes and thrombocytes were not included. Nevertheless, this is one of the largest prospective studies of a community sample, with the hitherto longest follow-up period. It is the first study to investigate the full range of mood disorder subtypes. Forth, with only 55 subjects with a lifetime history of BPD at baseline and only 13 subjects who had developed this disorder during the follow-up we did not have adequate power to test the longitudinal associations between this disorder and inflammatory markers.

These prospective data from a large community sample show that unidirectional association between current MDD subtypes with atypical features and increased hsCRP levels at a more than 5-year follow-up may be a consequence of this condition. Further prospective studies with repeated assessments of inflammatory markers earlier in the development of mood disorders are required to examine whether successful treatment of depression could lead to a decrease in inflammation and consequently cardiovascular risk.

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CONFLICTS OF INTEREST:

None.

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TABLE 1: Sociodemographic, Medication, Health-Related Behaviors, Physical Risk Factors for Cardiovascular Disorders and Inflammatory markers by lifetime mood disorders at baseline (n=3118)

	Bipolar disorder		MDD		Major depressive disorder subtypes								No Mood Disorders		*p*-value [a]
					Combined MDD		Atypical MDD		Melancholic MDD		Unspecified MDD				
	n = 55		n = 1367		n = 171		n = 206		n = 362		n = 628		n = 1696		
	Current n = 2		Current n = 213		Current n = 36		Current n = 47		Current n = 49		Current n = 81				
	Remitted n = 53		Remitted n = 1154		Remitted n = 135		Remitted n = 159		Remitted n = 313		Remitted n = 547				
Sociodemographics															
Length of follow-up, mean (SD)	5.62	(0.71)	5.51	(0.59)	5.46	(0.61)	5.51	(0.55)	5.53	(0.57)	5.51	(0.61)	5.54	(0.63)	*0.568*[b]
Sex, n (%)															
Female	26	(47.27)	899	(65.76)	123	(71.93)	148	(71.84)	245	(67.68)	383	(60.99)	748	(44.10)	***<.0001***
Male	29	(52.73)	468	(34.24)	48	(28.07)	58	(28.16)	117	(32.32)	245	(39.01)	948	(55.90)	
Age, mean (SD)	51.15	(8.43)	50.33	(8.71)	50.64	(8.84)	49.56	(8.68)	50.60	(8.69)	50.35	(8.70)	51.53	(8.87)	***0.007***[b]
Socio-economic status, mean (SD)	3.33	(1.29)	3.42	(1.26)	3.31	(1.24)	3.34	(1.21)	3.39	(1.34)	3.50	(1.23)	3.42	(1.28)	*0.381*[b]
Ethnicity, n (%)															
Caucasian	55	(100.00)	1251	(91.51)	160	(93.57)	191	(92.72)	331	(91.44)	569	(90.61)	1575	(92.87)	*0.119*
Other	0	(0.00)	116	(8.49)	11	(6.43)	15	(7.28)	31	(8.56)	59	(9.39)	121	(7.13)	
Marital status, n (%)															
Living alone	25	(45.45)	547	(40.01)	65	(38.01)	93	(45.15)	153	(42.27)	236	(37.58)	429	(25.29)	***<.0001***
Living in couple	30	(54.55)	820	(59.99)	106	(61.99)	113	(54.85)	209	(57.73)	392	(62.42)	1267	(74.71)	
Comorbid disorders, n (%)															
Anxiety disorders	22	(40.00)	340	(24.87)	56	(32.75)	51	(24.76)	94	(25.97)	139	(22.13)	204	(12.03)	***<.0001***
Substance use disorders	13	(23.64)	218	(15.95)	31	(18.13)	22	(10.68)	60	(16.57)	105	(16.72)	240	(14.15)	***0.060***
Medication, n (%)															
Antidipressants	28	(50.91)	522	(38.19)	86	(50.29)	91	(44.17)	176	(48.62)	169	(26.91)	90	(5.31)	***<.0001***
Mood stabilizers	12	(21.82)	8	(0.59)	1	(0.58)	1	(0.49)	5	(1.38)	1	(0.16)	2	(0.12)	***<.0001***
Antipsychotics	10	(18.18)	32	(2.34)	8	(4.68)	4	(1.94)	9	(2.49)	11	(1.75)	9	(0.53)	***<.0001***
Aspirin	10	(18.18)	121	(8.85)	17	(9.94)	24	(11.65)	33	(9.12)	47	(7.48)	130	(7.67)	***0.030***
Statins	6	(10.91)	93	(6.80)	12	(7.02)	14	(6.80)	23	(6.35)	44	(7.01)	132	(7.78)	*0.819*
Health-related behaviors, n (%)															
Former smoking	21	(38.18)	441	(32.26)	49	(28.65)	64	(31.07)	112	(30.94)	216	(34.39)	569	(33.55)	*0.557*
Current smoking	21	(38.18)	417	(30.50)	62	(36.26)	54	(26.21)	102	(28.18)	199	(31.69)	423	(24.94)	***0.001***
Physical inactivity	21	(38.18)	600	(43.89)	78	(45.61)	97	(47.09)	148	(40.88)	277	(44.11)	737	(43.46)	*0.681*
Biological risk factors															
Body mass index, mean (SD)	26.46	(4.99)	25.13	(4.47)	25.66	(5.21)	26.46	(4.83)	24.56	(4.16)	24.87	(4.20)	25.46	(4.23)	***0.000***[b]
Diabetes, n (%)	3	(5.45)	57	(4.17)	11	(6.43)	9	(4.37)	9	(2.49)	28	(4.46)	88	(5.19)	*0.293*
Dyslypidemia, n (%)	20	(36.36)	406	(29.70)	54	(31.58)	60	(29.13)	104	(28.73)	188	(29.94)	563	(33.20)	*0.379*
Hypertension, n (%)	13	(23.64)	364	(26.63)	44	(25.73)	67	(32.52)	95	(26.24)	158	(25.16)	525	(30.96)	***0.036***
Inflammatory markers at baseline, Median (IQR)															
Interleukin-6	1.24	(0.35-2.64)	1.19	(0.50-3.04)	1.25	(0.63-3.37)	1.29	(0.56-3.25)	1.22	(0.52-2.73)	1.13	(0.45-3.04)	1.34	(0.60-3.36)	*0.106*
Tumor Necrosis Factor-α	2.52	(1.65-3.91)	2.69	(1.62-4.29)	2.54	(1.62-4.17)	2.89	(1.71-4.81)	2.72	(1.63-4.26)	2.61	(1.57-4.26)	2.87	(1.85-4.47)	*0.067*
High-sensitivity C-Reactive protein	1.30	(0.70-3.10)	1.00	(0.50-2.10)	0.90	(0.50-2.20)	1.10	(0.60-2.60)	1.00	(0.50-2.20)	1.00	(0.50-2.00)	1.00	(0.50-2.20)	***0.030***
Inflammatory markers at follow-up, Median (IQR)															
Interleukin-6	2.49	(1.25-6.10)	2.31	(0.89-7.79)	2.44	(0.73-5.54)	2.51	(0.80-8.92)	2.05	(0.85-7.27)	2.35	(0.93-8.02)	2.82	(0.98-8.83)	*0.100*
Tumor Necrosis Factor-α	5.35	(2.98-7.86)	4.48	(2.43-8.07)	4.52	(2.17-7.51)	4.25	(2.33-9.14)	4.56	(2.80-7.89)	4.53	(2.42-8.09)	4.72	(2.52-8.27)	*0.826*
High-sensitivity C-Reactive protein	1.60	(0.90-3.40)	1.10	(0.60-2.50)	1.20	(0.70-2.60)	1.40	(0.70-3.20)	1.10	(0.60-2.70)	1.10	(0.50-2.35)	1.20	(0.60-2.50)	***0.018***

Abbreviations: SD = standard deviation; MDD = major depressive disorder; IQR=Interquartile range (the 25% and 75% are provided).

Median and IQR of inflammatory markers were not logarithmically transformed (n IL-6, TNF- α = 2796, n hsCRP = 2896).

[a] Chi-square Test; b Kruskal-Wallis Test.

TABLE 2: Associations between current and remitted mood disorders at baseline and inflammatory markers at follow-up

	Interleukin 6 [pg/ml]			Tumor Necrosis Factor-α [pg/ml]			hs C-Reactive Protein [mg/l]		
	β[a]	(95% CI)	*p-value*	β[a]	(95% CI)	*p-value*	β[a]	(95% CI)	*p-value*
Current diagnoses									
Bipolar Disorder	-1.29	(-3.51-0.93)	*0.256*	0.17	(-1.22-1.56)	*0.810*	-0.61	(-1.66-0.43)	*0.251*
Major Depressive Disorder	-0.10	(-0.33-0.14)	*0.429*	-0.06	(-0.21-0.09)	*0.427*	**0.12**	**(0.01-0.22)**	***0.037***
MDD Combined Subtype	**-0.69**	**(-1.23/-0.14)**	***0.014***	-0.27	(-0.61-0.08)	*0.127*	**0.33**	**(0.07-0.59)**	***0.011***
MDD Atypical Subtype	-0.12	(-0.62-0.37)	*0.627*	0.04	(-0.27-0.35)	0.809	**0.36**	**(0.14-0.58)**	***0.002***
MDD Melancholic Subtype	-0.07	(-0.55-0.42)	*0.785*	-0.18	(-0.48-0.12)	*0.247*	-0.09	(-0.31-0.13)	*0.406*
MDD Unspecified Subtype	0.19	(-0.19-0.56)	0.322	0.06	(-0.17-0.29)	*0.622*	-0.02	(-0.19-0.16)	*0.855*
Remitted diagnoses									
Bipolar Disorder	0.14	(-0.33-0.60)	*0.567*	0.09	(-0.20-0.38)	*0.550*	0.18	(-0.04-0.39)	*0.111*
Major Depressive Disorder	-0.07	(-0.19-0.06)	*0.300*	-0.00	(-0.08-0.07)	*0.925*	-0.03	(-0.08-0.03)	*0.384*
MDD Combined Subtype	-0.05	(-0.34-0.24)	*0.740*	0.00	(-0.18-0.19)	*0.984*	-0.08	(-0.22-0.05)	0.226
MDD Atypical Subtype	-0.02	(-0.29-0.24)	*0.856*	-0.11	(-0.28-0.06)	0.189	-0.03	(-0.16-0.10)	*0.640*
MDD Melancholic Subtype	-0.19	(-0.38-0.01)	*0.069*	0.06	(-0.07-0.18)	*0.379*	0.01	(-0.08-0.10)	*0.781*
MDD Unspecified Subtype	0.03	(-0.13-0.19)	*0.691*	-0.00	(-0.10-0.10)	*0.954*	-0.02	(-0.09-0.06)	*0.675*

Abbreviations: β = β-estimator; CI = confidence interval; MDD = major depressive disorder.
Models adjusted for the corresponding inflammatory marker at baseline, "No mood disorders" considered as the comparison group.
[a] multiple regression with logarithmically transformed cytokine (n = 2796) or hsCRP concentrations (n = 2896).
Statistically significant results are in bold.
p-values are in italic.

TABLE 3: Adjusted associations between current and remitted mood disorders at baseline and inflammatory markers at follow-up

	Interleukin 6 [pg/ml]			Tumor Necrosis Factor-α [pg/ml]			hs C-Reactive Protein [mg/l]		
	β[a]	(95% CI)	*p-value*	β[a]	(95% CI)	*p-value*	β[a]	(95% CI)	*p-value*
Current diagnoses									
Bipolar Disorder	--	--	--	--	--	--	--	--	--
MDD Combined Subtype	**-0.74**	**(-1.30\-0.18)**	***0.010***	-0.26	(-0.61-0.09)	*0.141*	**0.29**	**(0.03-0.55)**	***0.026***
MDD Atypical Subtype	-0.17	(-0.67-0.34)	*0.521*	0.04	(-0.28-0.35)	*0.814*	**0.32**	**(0.10-0.55)**	***0.005***
MDD Melancholic Subtype	-0.14	(-0.64-0.35)	*0.573*	-0.13	(-0.44-0.18)	*0.412*	-0.10	(-0.33-0.12)	*0.362*
MDD Unspecified Subtype	0.14	(-0.25-0.52)	0.478	0.08	(-0.16-0.32)	*0.521*	-0.01	(-0.19-0.16)	*0.889*
Remitted diagnoses									
Bipolar Disorder	0.04	(-0.46-0.55)	*0.872*	-0.01	(-0.32-0.30)	*0.954*	0.13	(-0.10-0.37)	*0.261*
MDD Combined Subtype	-0.13	(-0.44-0.18)	*0.415*	-0.01	(-0.20-0.18)	*0.916*	-0.09	(-0.23-0.05)	*0.202*
MDD Atypical Subtype	-0.10	(-0.38-0.19)	*0.499*	-0.10	(-0.28-0.08)	*0.268*	-0.04	(-0.17-0.09)	*0.552*
MDD Melancholic Subtype	**-0.23**	**(-0.45\-0.02)**	***0.036***	0.06	(-0.07-0.20)	*0.372*	0.03	(-0.07-0.13)	*0.517*
MDD Unspecified Subtype	-0.04	(-0.21-0.13)	*0.649*	0.00	(-0.10-0.11)	*0.970*	0.00	(-0.08-0.08)	*0.983*

Abbreviations: β = β-estimator; CI = confidence interval; MDD = major depressive disorder.
Models adjusted for the corresponding inflammatory marker at baseline, length of follow-up, socio-demographic variables (age, gender, socio-economic status, ethnicity and marital status), medications, comorbid mental disorders (anxiety and substance use disorders), behavioral cardiovascular risk factors (physical activity and smoking status) and physical cardiovascular risk factors (BMI, diabetes, hypertension and dyslipidemia) at baseline. "No mood disorders" considered as the comparison group.
Associations between inflammatory markers and a current diagnosis of bipolar disorder could not be assessed due to small sample size.
[a] Multiple regression with logarithmically transformed cytokine (n = 2797) or hsCRP concentrations (n = 2896).

TABLE 4: Associations between inflammatory markers at baseline and mood disorders at follow-up (n=2580)

Levels of Inflammatory marker at baseline	**Bipolar disorder** n = 13			**MDD** n = 608			**MDD Combined Subtype** n = 67			**MDD Atypical Subtype** n = 129			**MDD Melancholic Subtype** n = 155			**MDD Unspecified Subtype** n = 257		
	OR	(95% CI)	*p-value*	OR	(95% CI)	*p-value*	OR	(95% CI)	*p-value*	OR	(95% CI)	*p-value*	OR	(95% CI)	*p-value*	OR	(95% CI)	*p-value*
Model 1																		
IL-6 [pg/ml]	0.68	(0.37-1.25)	*0.215*	0.96	(0.88-1.06)	*0.436*	0.95	(0.74-1.22)	*0.703*	0.87	(0.73-1.05)	*0.153*	1.04	(0.88-1.22)	*0.674*	0.96	(0.84-1.09)	*0.497*
TNF-α [pg/ml]	0.75	(0.40-1.41)	*0.372*	**0.86**	**(0.78-0.95)**	***0.002***	1.02	(0.80-1.30)	*0.889*	**0.83**	**(0.69-1.00)**	***0.046***	0.90	(0.76-1.06)	*0.214*	**0.86**	**(0.75-0.98)**	***0.023***
hsCRP [mg/l]	0.98	(0.56-1.69)	*0.929*	0.93	(0.85-1.03)	*0.148*	1.03	(0.81-1.32)	*0.786*	0.98	(0.82-1.18)	*0.849*	0.87	(0.74-1.03)	*0.101*	0.94	(0.82-1.07)	*0.312*
Model 2																		
IL-6 [pg/ml]	0.74	(0.35-1.56)	*0.431*	1.01	(0.91-1.12)	*0.857*	0.94	(0.72-1.23)	*0.642*	0.88	(0.72-1.08)	*0.221*	1.08	(0.91-1.28)	*0.386*	1.02	(0.88-1.17)	*0.826*
TNF-α [pg/ml]	0.75	(0.34-1.63)	*0.467*	**0.85**	**(0.77-0.95)**	***0.003***	1.05	(0.81-1.36)	*0.713*	0.85	(0.69-1.04)	*0.117*	0.88	(0.74-1.05)	*0.162*	**0.86**	**(0.74-0.99)**	***0.034***
hsCRP [mg/l]	1.10	(0.57-2.12)	*0.772*	0.90	(0.81-1.00)	*0.054*	1.05	(0.80-1.38)	*0.704*	0.88	(0.72-1.08)	*0.219*	0.94	(0.79-1.14)	*0.544*	0.90	(0.78-1.04)	*0.143*

Abbreviations: IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor-α; hsCRP = high sensitivity C-Reactive Protein; OR = odds ratio; CI = confidence interval; MDD = major depressive disorder.

Model 1: adjusted for the corresponding mental disorder at baseline.

Model 2: adjusted for the corresponding mental disorder at baseline, length of follow-up, socio-demographic variables (gender, age, socio-economic status, ethnicity and marital status), medications, health-related behaviors (former smoker, current smoker and physical inactivity), and physical cardiovascular risk factors (body mass index, diabetes, dyslipidemia and hypertension) at baseline.