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Associations between mood, anxiety or substance use disorders and inflammatory markers after adjustment for multiple covariates in a population-based study

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Abstract

Inflammation is one possible mechanism underlying the associations between mental disorders and cardiovascular diseases (CVD). However, studies on mental disorders and inflammation have yielded inconsistent results and the majority did not adjust for potential confounding factors. We examined the associations of several pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and high sensitive C-reactive protein (hsCRP) with lifetime and current mood, anxiety and substance use disorders (SUD), while adjusting for multiple covariates. The sample included 3'719 subjects, randomly selected from the general population, who underwent thorough somatic and psychiatric evaluations. Psychiatric diagnoses were made with a semi-structured interview. Major depressive disorder was subtyped into "atypical", "melancholic", "combined atypical-melancholic" and "unspecified". Associations between inflammatory markers and psychiatric diagnoses were assessed using multiple linear and logistic regression models. Lifetime bipolar disorders and atypical depression were associated with increased levels of hsCRP, but not after multivariate adjustment. After multivariate adjustment, SUD remained associated with increased hsCRP levels in men (β= 0.13 (95% CI: 0.03,0.23)) but not in women. After multivariate adjustment, lifetime combined and unspecified depression were associated with decreased levels of IL-6 (β= -0.27 (-0.51,-0.02); β= -0.19 (-0.34,-0.05), respectively) and TNF-α (β= -0.16 (-0.30,-0.01); β= -0.10 (-0.19,-0.02), respectively), whereas current combined and unspecified depression were associated with decreased levels of hsCRP (β= -0.20 (-0.39,-0.02); β= -0.12 (-0.24,-0.01), respectively). Our data suggest that the significant associations between increased hsCRP levels and mood disorders are mainly attributable to the effects of comorbid disorders, medication as well as behavioral and physical CVRFs.

Key words: C-reactive protein; pro-inflammatory cytokines; mood disorders, depression subtypes; anxiety disorders; substance use disorders.

1. Introduction

Chronic inflammation as part of the innate immune response has been postulated to be one mechanism (Baune et al., 2012; Dinan, 2009; Vogelzangs et al., 2013) underlying the well-documented associations of mental disorders with cardiovascular risk factors (CVRFs) (Glaus et al., 2013; van Reedt Dortland et al., 2013) and cardiovascular diseases (CVD) (Baune et al., 2012). Pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 or tumor necrosis factor (TNF)-α (Dowlati et al., 2010; Mota et al., 2013) induce the production of acute-phase proteins including the C-reactive protein (CRP) (Maes et al., 1997), which is a common marker of underlying low-grade inflammation (Ford & Erlinger, 2004). Cytokines and the CRP have been found to be associated with CVRFs such as diabetes (Marques-Vidal et al., 2012a), overweight (Marques-Vidal et al., 2012b) and smoking (Yanbaeva et al., 2007), as well as with several mental disorders.

The bulk of research on mental disorders and inflammatory markers has focused on major depressive disorder (MDD) revealing complex association pictures depending on the type of the sample and the covariates analyses adjusted for. A recent meta-analyses of clinical studies has documented higher concentrations of circulating IL-6 and TNF-α among depressed subjects compared to healthy controls (Liu et al., 2012), whereas a meta-analysis of a small set of community studies revealed inconclusive results (Kuo et al., 2005). Another meta-analysis including both clinical and community studies supported associations between inflammatory markers and depression in clinical and to a lower degree also in community studies (Howren et al., 2009). However, the strength of these associations largely varied in function of the instruments used to assess depression and the covariates the analyses were adjusted for. In several studies, the association between inflammation and depression was no longer statistically significant after adjustment for covariates, although the number of covariates considered was often limited (Vogelzangs et al., 2012; Duivis et al., 2011; Douglas et al., 2004). Moreover, the results of one of the few studies that adjusted for multiple covariates suggest that the distinction between lifetime and current depression is important to determine whether the increase of inflammation markers persists after the remission of a depressive episode (Whooley et al., 2008). In contrast to the expectation, this study revealed lower CRP and IL-6 levels in patients with current depression than

in those with lifetime depression (Whooley et al., 2008). Heterogeneity of depression (Schmidt et al., 2011) is another potential source of the large variety of results across previous research. However, the use of depression scales rather than diagnostic interviews in the large majority of previous studies impeded them to subtype depression. The few studies that subtyped depression in clinical patients generally suggested differential associations of depression subtypes with inflammation markers. Indeed, non-melancholic depression has been found to be associated with increased levels of IL-1β (Kaestner et al., 2005) and chronic atypical depression with increased levels of the CRP, IL-6 and TNF-α (Lamers et al., 2012), whereas melancholic patients did not reveal increased levels of inflammatory markers as compared to non-depressed individuals (Rothermundt et al., 2001). Similarly, a community based study found levels of CRP to be higher in subjects suffering from atypical depression compared to non-atypical and non depressive subjects, although there were no differences between the two latter groups (Hickman et al., 2013). In contrast, a recent clinical study did not provide evidence of higher levels of IL-6 and TNF-α in atypical as compared to melancholic depressives (Yoon et al., 2012), whereas another small clinical study (Rudolf et al., 2014) documented higher levels of IL-6 in patients with atypical MDD than in patients with typical MDD and controls. These differences remained significant after adjustment for weight in the latter study, whereas in the study of Lamers et al. (Lamers et al., 2012), the between-group differences remained significant only for TNF-α but not for the CRP and IL-6 after adjustment for the body mass index (BMI).

Regarding bipolar disorder, a recent meta-analysis of 30 studies also showed significant elevations of IL-6 and TNF-α in subjects exhibiting this disorder as compared to healthy controls (Modabbernia et al., 2013). Similarly, increased levels of high sensitive CRP (hsCRP) were found during acute episodes of mania (Cunha et al., 2008). In contrast to mood disorders, studies on the association between anxiety disorders or substance use disorders (SUD) and inflammatory markers are still rare. Recent studies revealed elevated levels of inflammatory markers in subjects with PTSD (von Kanel et al., 2007; Gill et al., 2009; Spitzer et al., 2010) and in male but not female subjects with current anxiety disorders (Vogelzangs et al., 2013), whereas decreased CRP and IL-6 levels were observed in women with current social phobia (Vogelzangs et al., 2013). A

longitudinal study found generalized anxiety disorder (GAD) to be associated with an increased CRP level, but this association was attributable to health-related factors such as BMI and medication use (Copeland et al., 2012). Concerning substance use disorders (SUD), our group previously reported an association between moderate alcohol consumption and lower levels of IL-6 and TNF-α (Marques-Vidal et al., 2012c), whereas a recent review concluded that the levels of pro-inflammatory cytokines are increased in patients suffering from chronic alcoholism (Achur et al., 2010). Among the very few studies that examined the role of other SUD, Costello et al. (Costello et al., 2013) showed a prospective positive association between the CRP level and any substance abuse or dependence in the community and Nabati et al. (Nabati et al., 2013) found some elevated cytokines in opium addicts (e.g. Il-6) whereas others were diminished.

Given the and limitations and partially inconsistent findings of previous research, we aimed to further examine the associations between mood disorders and their subtypes, anxiety and substance use disorders and inflammation markers (CRP, IL-1β, IL-6, TNF-α) in the community with serial adjustments for a wide array of covariates including socio-demographic characteristics, psychotropic medication, behavioral and physical CVRFs. Separate analyses were conducted for lifetime and current mental disorders.

2. Methods

2.1. Study population

The data of the present paper stem from CoLaus|PsyCoLaus (Preisig et al., 2009), a cohort study designed to study mental disorders and CVRFs/CVD in the general population. A total of 6'736 individuals (CoLaus), aged between 35 and 75 years, were initially recruited in 2003 in the city of Lausanne (Switzerland), based on the population registry of the city. In addition to anthropometric measures, DNA and plasma samples were collected for the study of genetic variants and biomarkers associated with CVRFs (Firmann et al., 2008). Subsequently, 67% of the participants of the CoLaus study in the age range of 35 to 66 years (N=5'535) agreed to take part in the psychiatric evaluation (PsyCoLaus), which resulted in a sample of 3'719 individuals who underwent

both the somatic/cardiovascular and psychiatric exams (Preisig et al., 2009). Ninety-two percent were Caucasians. The gender distribution of the PsyCoLaus sample (47% men) did not differ significantly from that of the general population in the same age range (Preisig et al., 2009). Among these 3'719 participants, 3'527 had measures of high-sensitivity CRP (hsCRP) and 3'478 of pro-inflammatory cytokines. Participants of PsyCoLaus and individuals who refused to participate had comparable scores on the General Health Questionnaire (GHQ-12 (Goldberg, 1972); French translation (Bettschart & Bolognini, 1996)), a self-rating instrument which assessed psychiatric symptoms at the physical exam.

The CoLaus and subsequently the PsyCoLaus study were both approved by the local Institutional Ethic's Committee. All participants gave written informed consent after having received a detailed description of the goal and funding of the study.

2.2. Measurements

2.2.1. Psychiatric evaluation

Mental disorders were assessed using the semi-structured Diagnostic Interview for Genetic Studies (DIGS (Nurnberger et al., 1994)). Interviewers were required to be master-level psychologists or psychiatrists, who were trained for two months. Training included rating tapes and supervised co-ratings. In order to provide supervision throughout the study, all interviews and diagnostic assignments were reviewed by an experienced senior psychologist.

The DIGS was developed by the National Institute of Mental Health Molecular Genetics Initiative (NIMH) to obtain a more precise assessment of phenotypes across a wide spectrum of DSM-IV Axis I criteria. The DIGS was completed with sections on anxiety disorders using the questions from the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L (Endicott & Spitzer, 1978)). The original DIGS section on nicotine consumption was expanded. The French translation of the DIGS (Leboyer et al., 1995) revealed excellent inter-rater reliability in terms of kappa and Yule's Y coefficients for major mood and psychotic disorders (Preisig et al., 1999), and for SUD (Berney et al., 2002); the 6-week test-retest reliability was lower but still in the fair to good range (Berney et al., 2002; Preisig et al., 1999). The anxiety sections of the French version of the SADS-LA also revealed satisfactory inter-rater and test-retest reliability (Leboyer et al., 1991).

Information from the depression section of the DIGS allowed for the categorization of lifetime MDD into four subtypes (Angst et al., 2006): 1) MDD with at least one atypical and one melancholic episode (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). For the definitions of MDD subtypes, we used the DSM-IV specifiers in a non-hierarchical way (see (Glaus et al., 2013)).

As the psychiatric investigation was conducted approximately one year after the somatic exam, we defined a current episode of depression as meeting criteria for MDD at the psychiatric evaluation and having a GHQ-12 score > 1, indicating clinically relevant distress at the time of the physical evaluation. Moreover, for the other psychiatric disorders, we considered diagnoses to be current if the subject described the disorder as ongoing at the time of the psychiatric investigation. Subjects with current diagnoses were also included in the categories of lifetime diagnoses in the present analyses.

Lifetime alcohol and drug abuse and dependence diagnoses were lumped together. The subjects with alcohol dependence (N=178) and those with alcohol abuse (n=187) acknowledged an intake of 30.1 and 19.5 drinks per week, respectively, during a period of regular consumption. Subjects with one or more lifetime drug disorder met criteria for cocaine, heroin, stimulant, sedative or hallucinogen abuse or dependence.

The DIGS also allows for the recording of information on psychotropic drug treatment over lifetime as well as on leisure time physical activity. The section on psychotropic drug treatment took into account all types of antidepressants, mood stabilizers (lithium and anti-epileptics) and all antipsychotics. A subject was considered to be physically inactive when there was no indication of regular physical exercise at least once a week at the time of the psychiatric evaluation.

Socio-economic status (SES) was assessed using the Hollingshead scale (Hollingshead, 1975).

2.2.2. Physical and biochemical evaluation

HsCRP was assessed 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 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. Cytokine levels were measured using a multiplexed particle-based flow cytometric cytokine assay (Marques-Vidal et al., 2011). Lower detection limits (LOD) for IL-1β, IL-6 and TNF-α were 0.2 pg/ml. Good agreement between signal and cytokine was found within the assay range ($R^2 \geq 0.99$).

Anthropometric measures (body weight, height, waist and hip circumferences) were obtained to calculate the BMI (mass in kg divided by the height in meters raised to the square) (Firmann et al., 2008). A diagnosis of hypertension was assigned in the case of a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg, or if drug treatment was prescribed for hypertension. Venous blood samples were drawn from each participant after an overnight fast in order to measure the levels of glucose, HDL-cholesterol, LDL-cholesterol and triglycerides. Diabetes was diagnosed when a fasting blood glucose ≥ 7mmol/l was measured or when the subject was treated for diabetes. Diagnostic criteria for dyslipidemia were: HDL-cholesterol < 1 mmol/l, or LDL-cholesterol ≥ 4.1 mmol/l, or triglycerides ≥ 2.2 mmol/l, or when treated with a lipid-lowering drug. Regular nicotine consumption was defined as a current or past history of regular daily consumption of at least 10 cigarettes.

2.3. Statistical analysis

Statistical analyses were conducted using the Statistical Analysis System, version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). Descriptive data for demographic characteristics, psychiatric disorders and inflammatory markers were derived for the total sample and by gender. Comparisons between men and women were conducted using Student's t-test, Wilcoxon-Mann-Whitney test or chi-square tests as appropriate. Associations between mental disorders and hsCRP, IL-6 and TNF-α outcome levels 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., 9.5% of values

for IL-6, 0.7% 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. Subsequently, a multiple linear regression was performed on log-transformed observed values. Given that as many as 37.1% of the values of IL-1β were below the LOD, we dichotomized this variable at the median and applied logistic regression models. Five models of increasing complexity were computed. Interactions between specific mental disorders and gender were tested for all inflammation markers. In case of significant interactions, stratified analyses were performed by gender. A first series of models (Model 1) included one single mental disorder at a time as the independent variable, adjusted for socio-demographic characteristics (gender, age and SES). Age of subjects was divided by its standard deviation to improve its comparability to the other covariates (i.e. the OR for age described the increase in odds per increase of one standard deviation). Model 2 included all mental disorders simultaneously in order to determine the association of specific mental disorders with inflammation markers, adjusting for all comorbid disorders. Model 3 was further adjusted for the effects of psychotropic medication (antidepressants, mood stabilizers and antipsychotics), Model 4 for the effects of behavioral CVRFs (physical inactivity and smoking) and Model 5 for all the previous covariates as well as for the well-established physical CVRFs (BMI, diabetes, dyslipidemia and hypertension). P-values were not adjusted for multiple testing because the hypothesized associations between mental disorders and inflammatory markers were specified a priori.

3. Results

The characteristics of the participants are presented in Table 1. Women were older than men, had a lower SES, lower levels of IL-6 and TNF-α, and higher lifetime rates of MDD, MDD subtypes and anxiety disorders. A similar pattern emerged for current mental disorders, except for unspecified MDD where no gender differences were observed. In contrast, women had less lifetime and current SUD than men

All covariates used as adjustments in the models, except for psychotropic medications, were associated with pro-inflammatory cytokines or hsCRP (table e-1 published online). First, associations between lifetime or current mental disorders and inflammatory markers adjusted only for socio-demographic characteristics are presented in Table 2. Significant interactions between mental disorders and gender emerged for lifetime bipolar disorder (BPD) regarding IL-6 (β=0.99, 95% CI: (0.20,1.78); men: β=-0.83, (-1.35,-0.31); women: β=0.16, (-0.43,0.75)) and SUD regarding hsCRP levels (β=-0.32, (-0.52,-0.12); men: β=0.19, (0.09,0.30); women: β=-0.13, (-0.31,0.04)). In addition, lifetime BPD and the atypical MDD subtype were associated with increased levels of hsCRP. The hsCRP level in subjects exhibiting the lifetime atypical MDD subtype was significantly higher than those with the other MDD subtypes as indicated by the β-estimate, which lay above the upper bound of the 95% confidence interval of the estimates for all the other MDD subtypes. In contrast, lifetime and current anxiety disorders were associated with decreased levels of hsCRP. Neither the IL-1β nor the TNF-α revealed associations with lifetime or current mental disorders. Similar to the models adjusted for socio-demographic characteristics, the models adjusted for the other covariates (Model 2 to Model 5: Tables 3 and 4) revealed significant interactions by gender: lifetime BPD regarding IL-6 (Model 5: interaction term β= 0.98, (0.15,1.80) and SUD regarding hsCRP levels (Model 5: β= -0.29, (-0.48,-0.10)). Indeed, men compared to women with lifetime BPD had decreased IL-6 levels (β= -0.84, (-1.45,-0.24) vs. β= -0.13, (-0.76,0.50)), whereas men compared to women with lifetime SUD had increased hsCRP levels (β= 0.13, (0.03,0.23) vs. β= -0.11, (-0.27,0.06)).

In addition, decreased levels of IL-6 and TNF-α were found to be associated with some mental disorders (Tables 3 and 4). Indeed, lifetime BPD was found to be associated with decreased levels of TNF-α even after full adjustments. Furthermore, BPD was associated with increased levels of hsCRP, but no longer after adjustment for physical CVRFs. The combined MDD subtype was associated with a decreased level of IL-6 after full adjustments, and with a decreased level of TNF-α when the model was adjusted for behavioral and physical CVRFs. Unspecified MDD was associated with decreased levels of IL-6 and TNF-α in all four models, whereas lifetime atypical MDD was no longer associated with hsCRP in any of the four models. Finally, lifetime anxiety disorders were still associated with decreased levels of hsCRP but no longer after adjustment for

physical CVRFs. Concerning the associations between current mental disorders and inflammatory markers (Table 4), pro-inflammatory cytokines were not associated with any mental disorder. However, combined MDD was associated with lower levels of hsCRP in the final model. Melancholic and anxiety disorders were associated with decreased levels of hsCRP until Model 4, but no longer after adjustment for physical CVRFs (Model 5). Unspecified MDD remained negatively associated with hsCRP throughout Models 2 to 5. Finally, associations between pro-inflammatory markers and a current diagnosis of BPD could not be assessed due to the small sample size.

4. Discussion

The present study is, to our knowledge, the first to simultaneously assess the associations between several inflammatory markers and a large array of DSM-IV Axis-I disorders and subtypes of MDD in the community with serial adjustments for multiple covariates. The study has revealed complex association patterns between mental disorders and inflammatory markers, which have shown a large variance across disorders and differed partially according to gender and the covariates adjusted for. The major findings, which were more prominent using lifetime than current diagnoses, were: 1) the associations between lifetime BPD or the atypical MDD subtype with increased hsCRP levels are no longer statistically significant after adjustment for multiple covariates; 2) lifetime BPD is associated with lower IL-6 levels in men and with lower TNF-α levels in both genders after adjustment for covariates; 3) the combined and unspecified subtypes of lifetime MDD are also associated with lower levels of IL-6 and TNF-α, and 4) lifetime SUD is associated with increased hsCRP levels in men but not in women.

4.1. BPD and inflammation

Our data provided evidence for positive and negative associations between BPD and inflammatory markers. First, BPD was associated with lower TNF-α levels after adjustment for multiple covariates and with lower IL-6 levels in men. Conversely, we observed a positive association

between BPD and hsCRP levels. However, the cross-sectional nature of our data precludes conclusions regarding the direction of causality. Accordingly, the fact that the association between BPD and hsCRP levels was no longer statistically significant after adjustment for physical CVRFs could be explained by an increase of inflammation markers in bipolar subjects either as a consequence of or as a predisposing factor to physical CVRFs.

4.2. Depression and inflammation

Our community data provide partial support to recent clinical findings (Kaestner et al., 2005; Lamers et al., 2012; Rothermundt et al., 2001; Rudolf et al., 2014) that suggested differential associations between subtypes of MDD and inflammatory markers. Indeed, after adjustment for demographic factors, subjects exhibiting the atypical MDD subtype revealed higher hsCRP levels than those with other depression subtypes or without depression. However, similar to the study of Lamers et al (Lamers et al., 2012), which relied on severely affected patients with chronic depression, this association was no longer statistically significant after adjustment for multiple covariates including physical CVRFs. Accordingly, atypical depression could contribute to inflammation via facilitating adverse health behaviors or the accumulation of physical CVRFs, which have been shown to be associated with elevated inflammation (Marques-Vidal et al., 2012b; Marques-Vidal et al., 2012d; Lamers et al., 2012). The lower magnitude of the association between depression and inflammation markers after adjustment for CVRFs including BMI is also in line with a recent meta-analysis (Howren et al., 2009). However, the cross-sectional design of the present study does not allow us to assess the temporal sequence of the onset of depression subtypes, the increase of inflammation markers and the onset of CVRFs and to determine the role of inflammation in the strong association between the atypical depression subtype and CVRFs. Indeed, a third variable (covariate) such as BMI could be 1) a mediator of the association (atypical depression could lead to increase weight, which is associated with elevated inflammatory markers), 2) a confounder (an elevated BMI could predispose to both depression and elevated inflammatory markers), 3) a consequence of elevated inflammatory markers (if elevated

inflammatory markers predisposes to BMI increase), or 4) a condition predisposing to the mental disorder (elevated BMI could predispose to depression).

Interestingly, after adjustment for multiple covariates in our study the combined and unspecified MDD subtypes revealed negative associations with IL-6 and TNF-α, whereas the other MDD subtypes were not associated with any inflammatory markers. At least two previous studies already provided evidence for decreased levels of cytokines in depressed subjects (Whooley et al., 2008; Rothermundt et al., 2001). One explanation is that this could be due to decreased levels of monocytes found in depressed patients (Whooley et al., 2008). Secretion of IL-6 by monocytes is a major source of IL-6 concentration that can be measured in the circulation (Whooley et al., 2008). Another potential explanation is that elevated levels of cortisol are found in depressed compared to non-depressed subjects (Burke et al., 2005), and it is well known that cortisol has anti-inflammatory properties (Duivis et al., 2011). Elevated cortisol levels might particularly suppress pro-inflammatory cytokine production (Hansel et al., 2010).

4.3. Anxiety disorders and inflammation

In contrast to a previous clinical study (Vogelzangs et al., 2013), anxiety disorders were associated with lower hsCRP levels in our sample. However, this association was no longer statistically significant after adjustment for physical CVRFs, which suggests that this association is attributable to the low BMI of subjects with anxiety disorders (Glaus et al., 2013) and the strong positive association between the BMI and the hsCRP. The potential mediating effect of health-related factors in the association between anxiety disorders and CRP levels is consistent with findings of a previous community study (Copeland et al., 2012).

4.4. SUD and inflammation

The association between SUD and an increased hsCRP level remained significant in men even after multiple adjustments, which is in line with previous findings regarding increased levels of inflammation markers in alcoholics (Achur et al., 2010) and subjects with cannabis abuse or dependence (Costello et al., 2013). In drinkers, the increased level of pro-inflammatory cytokines

has been shown to be associated with chronic and acute alcohol-induced lever diseases, but also with a significant increase in spontaneous cytokine production (Achur et al., 2010). Similarly, chronic exposure to drugs may favor cytokine expression in the brain (Yamada 2008). Conversely, as suggested by the prospective community study of Costello et al. (Costello et al., 2013) a high CRP level is also a predictor of SUD.

4.5. Limitations

The results of the present study should be considered in the context of several limitations. First, the cross-sectional nature of the study precluded any statements about causality of the link between the studied mental disorders and inflammatory processes. Second, the use of a sample recruited in the general population limited our ability to study associations between inflammation markers and severe forms of mental illness (disorders that require inpatient or specialty clinics treatment), which are rare in the community. Third, we had to determine the presence of a current depression at the time of the assessment of inflammation using the GHQ scale, given the one-year interval between the assessment of inflammatory markers and the psychiatric evaluation.

4.6. Conclusion

In conclusion, our data suggest that the significant associations between increased hsCRP levels and BPD and the atypical MDD subtype, which were no longer statistically significant after adjustment for multiple covariates, are mainly attributable to the effects of comorbid disorders, medication as well as behavioral and physical CVRFs. Moreover, after adjustment for multiple covariates our data also provide evidence for negative associations between the combined and the unspecified MDD subtypes and inflammatory markers. Only SUD in men remained significantly associated with increased hsCRP levels after multivariate adjustment. Prospective studies are required to further elucidate the role of hsCRP levels in the complex association between mood disorders or SUD and CVRFs/CVD.

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Table e-1: Levels of pro-inflammatory proteins and covariates

			Interleukin-1β [pg/l]			Interleukin-6 [pg/ml]			TNF-α [pg/ml]			hsCRP [mg/l]			
		N	Median	IQR	p^a	Median	IQR	p^a	Median	IQR	p^a	N	Median	IQR	p^a
Demographic characteristics															
Gender	Men	1640	**0.39**	**(0.10,1.73)**		**1.42**	**(0.63,3.50)**		**2.92**	**(1.86,4.58)**		1684	1.00	(0.50,2.10)	
	Women	1838	**0.49**	**(0.10,2.00)**	***0.050***	**1.19**	**(0.49,3.12)**	***0.001***	**2.64**	**(1.63,4.26)**	***<0.001***	1843	1.10	(0.50,2.40)	*0.491*
Age			**-0.08**		***<.0001***[b]	**0.06**		***0.001***[b]	**0.11**		***<.000***[b]		**0.17**		***<.000***[b]
SES			0.00		*0.853*[b]	-0.02		*0.16*[b]	-0.01		*0.388*[b]		**-0.14**		***<.000***[b]
Lifetime diagnoses															
Bipolar	No	3416	0.44	(0.10,1.96)		1.28	(0.56,3.30)		2.80	(1.75,4.47)		3461	**1.00**	**(0.50,2.20)**	
	Yes	62	0.38	(0.10,0.91)	*0.500*	1.17	(0.35,2.59)	*0.113*	2.45	(1.55,3.88)	*0.099*	66	**1.30**	**(0.70,3.10)**	***0.017***
Dysthymia	No	3404	0.44	(0.10,1.94)		1.28	(0.56,3.29)		2.78	(1.74,4.45)		3449	1.10	(0.50,2.30)	
	Yes	74	0.36	(0.10,2.35)	*0.423*	1.22	(0.45,2.60)	*0.486*	3.20	(2.01,5.09)	*0.269*	78	0.90	(0.50,1.90)	*0.343*
MDD	No	1969	0.45	(0.10,1.94)		**1.34**	**(0.59,3.38)**		**2.87**	**(1.85,4.47)**		1995	1.10	(0.50,2.30)	
	Yes	1509	0.42	(0.10,1.92)	*0.250*	**1.20**	**(0.50,3.16)**	***0.036***	**2.69**	**(1.62,4.34)**	***0.004***	1532	1.00	(0.50,2.25)	*0.161*
Combined MDD	No	3275	0.44	(0.10,1.93)		1.29	(0.56,3.27)		2.81	(1.76,4.46)		3324	1.10	(0.50,2.30)	
	Yes	203	0.38	(0.10,2.11)	*0.837*	1.15	(0.61,3.12)	*0.464*	2.48	(1.59,4.09)	*0.091*	203	1.00	(0.50,2.30)	*0.927*
Atypical MDD	No	3261	0.44	(0.10,1.94)		1.27	(0.56,3.24)		2.77	(1.74,4.42)		3309	1.00	(0.50,2.20)	
	Yes	217	0.37	(0.10,1.86)	*0.777*	1.49	(0.50,4.09)	*0.290*	2.96	(1.78,4.91)	*0.253*	218	1.20	(0.60,2.60)	*0.096*
Melancholic MDD	No	3059	0.44	(0.10,1.94)		1.28	(0.56,3.31)		2.80	(1.76,4.46)		3104	1.10	(0.50,2.20)	
	Yes	419	0.42	(0.10,1.94)	*0.812*	1.24	(0.54,2.87)	*0.521*	2.75	(1.61,4.32)	*0.313*	423	1.00	(0.50,2.30)	*0.383*
Unspecified MDD	No	2808	0.44	(0.10,1.94)		**1.32**	**(0.59,3.29)**		**2.83**	**(1.78,4.47)**		2839	**1.10**	**(0.50,2.30)**	
	Yes	670	0.43	(0.10,1.92)	*0.340*	**1.12**	**(0.45,3.06)**	***0.021***	**2.61**	**(1.59,4.29)**	***0.013***	688	**1.00**	**(0.50,2.10)**	***0.046***
Anxiety disorders any	No	2848	0.45	(0.10,1.98)		1.29	(0.57,3.30)		2.81	(1.76,4.43)		2896	**1.10**	**(0.50,2.30)**	
	Yes	630	0.42	(0.10,1.82)	*0.489*	1.24	(0.50,3.18)	*0.198*	2.66	(1.69,4.49)	*0.318*	631	**1.00**	**(0.50,2.10)**	***0.019***
Substance use disorders	No	2939	0.44	(0.10,1.94)		**1.26**	**(0.54,3.16)**		**2.75**	**(1.73,4.36)**		2976	1.00	(0.50,2.20)	
	Yes	539	0.43	(0.10,1.77)	*0.954*	**1.43**	**(0.64,3.78)**	***0.030***	**2.98**	**(1.78,4.76)**	***0.041***	551	1.10	(0.60,2.40)	*0.173*
Current diagnoses															
Bipolar	No	3476	0.44	(0.10,1.94)		1.28	(0.56,3.27)		2.79	(1.75,4.45)		3525	**1.10**	**(0.50,2.30)**	
	Yes	2	0.25	(0.10,0.39)	*0.404*	2.30	(2.21,2.39)	*0.411*	1.18	(1.04,1.31)	*0.062*	2	**5.50**	**(3.40,7.60)**	***0.040***
Dysthymia	No	3458	0.44	(0.10,1.94)		1.28	(0.56,3.26)		2.79	(1.74,4.44)		3508	1.10	(0.50,2.30)	
	Yes	20	0.46	(0.10,1.64)	*0.970*	1.86	(0.66,7.97)	*0.265*	3.23	(1.89,5.34)	*0.438*	19	0.90	(0.70,2.60)	*0.962*
MDD	No	2838	0.42	(0.10,1.88)		1.27	(0.56,3.24)		2.81	(1.76,4.42)		2907	**1.10**	**(0.50,2.30)**	
	Yes	640	0.48	(0.10,2.13)	*0.386*	1.34	(0.60,3.49)	*0.357*	2.72	(1.66,4.51)	*0.639*	620	**0.95**	**(0.50,2.20)**	***0.022***
Combined MDD	No	3376	0.44	(0.10,1.94)		1.29	(0.56,3.27)		2.80	(1.75,4.45)		3429	1.10	(0.50,2.30)	

	Yes	102	0.38	(0.10,1.95)	*0.409*	1.14	(0.63,2.74)	*0.475*	2.46	(1.62,4.17)	*0.358*	98	0.95	(0.50,2.10)	*0.783*
Atypical MDD	No	3382	0.44	(0.10,1.96)		1.27	(0.56,3.25)		2.78	(1.75,4.43)		3437	1.10	(0.50,2.20)	
	Yes	96	0.40	(0.10,1.48)	*0.742*	1.67	(0.75,4.30)	*0.121*	3.10	(1.69,4.95)	*0.354*	90	1.20	(0.60,2.60)	*0.204*
Melancholic MDD	No	3287	0.43	(0.10,1.90)		1.28	(0.56,3.27)		2.79	(1.74,4.45)		3339	**1.10**	**(0.50,2.30)**	
	Yes	191	0.52	(0.10,2.34)	*0.092*	1.38	(0.54,3.04)	*0.716*	2.81	(1.85,4.45)	*0.832*	188	**0.90**	**(0.40,2.10)**	***0.048***
Unspecified MDD	No	3227	0.43	(0.10,1.90)		1.28	(0.56,3.24)		2.81	(1.75,4.44)		3283	**1.10**	**(0.50,2.30)**	
	Yes	251	0.48	(0.10,2.44)	*0.575*	1.28	(0.56,3.79)	*0.586*	2.64	(1.61,4.52)	*0.381*	244	**0.90**	**(0.40,2.10)**	***0.022***
Anxiety disorders any	No	3126	0.43	(0.10,1.95)		1.29	(0.57,3.29)		2.80	(1.75,4.43)		3176	**1.10**	**(0.50,2.30)**	
	Yes	352	0.45	(0.10,1.84)	*0.902*	1.19	(0.48,3.13)	*0.125*	2.62	(1.68,4.50)	*0.359*	351	**1.00**	**(0.50,2.00)**	***0.019***
Substance use disorders	No	3257	0.44	(0.10,1.96)		**1.27**	**(0.55,3.21)**		2.77	(1.75,4.38)		3310	1.00	(0.50,2.30)	
	Yes	221	0.35	(0.10,1.62)	*0.428*	**1.56**	**(0.71,4.32)**	***0.025***	3.22	(1.76,5.11)	*0.055*	217	1.30	(0.60,2.20)	*0.116*
Psychotropic medication															
Antidepressants	No	2759	0.43	(0.10,1.94)		1.27	(0.55,3.20)		2.79	(1.75,4.45)		2809	1.00	(0.50,2.20)	
	Yes	719	0.45	(0.10,1.92)	*0.691*	1.33	(0.62,3.59)	*0.157*	2.79	(1.74,4.40)	*0.989*	718	1.10	(0.60,2.40)	*0.179*
Mood stabilizers	No	3451	0.43	(0.10,1.94)		1.28	(0.56,3.27)		2.79	(1.75,4.45)		3500	1.10	(0.50,2.30)	
	Yes	27	0.50	(0.10,1.73)	*0.643*	1.49	(0.31,2.87)	*0.648*	3.28	(1.42,4.45)	*0.922*	27	1.20	(0.60,2.10)	*0.594*
Antipsychotics	No	3412	0.44	(0.10,1.94)		1.28	(0.56,3.24)		2.78	(1.75,4.43)		3463	1.00	(0.50,2.30)	
	Yes	66	0.46	(0.10,1.86)	*0.947*	1.42	(0.44,4.77)	*0.615*	3.21	(1.76,5.06)	*0.385*	64	1.45	(0.80,2.40)	*0.065*
Behavioral CVRFs															
Physical inactivity	No	2421	0.44	(0.10,1.99)		**1.23**	**(0.52,3.15)**		2.76	(1.74,4.35)		2446	**1.00**	**(0.50,2.10)**	
	Yes	1057	0.42	(0.10,1.82)	*0.425*	**1.43**	**(0.67,3.63)**	***0.003***	2.82	(1.75,4.66)	*0.189*	1081	**1.30**	**(0.60,2.70)**	***<0.001***
Smoking	No	1916	0.46	(0.10,1.94)		**1.15**	**(0.50,2.87)**		**2.70**	**(1.69,4.27)**		1968	**1.00**	**(0.50,2.00)**	
	Yes	1562	0.42	(0.10,1.93)	*0.941*	**1.48**	**(0.65,3.90)**	***<0.001***	**2.90**	**(1.85,4.73)**	***0.001***	1559	**1.20**	**(0.60,2.60)**	***<0.001***
Physical CVRFs															
Overweight/Obese	No	1804	**0.49**	**(0.10,2.11)**		**1.12**	**(0.47,3.07)**		**2.61**	**(1.66,4.14)**		1857	**0.70**	**(0.40,1.40)**	
	Yes	1674	**0.39**	**(0.10,1.70)**	***0.045***	**1.46**	**(0.68,3.47)**	***<0.001***	**3.00**	**(1.85,4.76)**	***<0.001***	1670	**1.60**	**(0.80,3.10)**	***<0.001***
Diabetes	No	3291	**0.46**	**(0.10,1.99)**		**1.26**	**(0.55,3.24)**		**2.77**	**(1.73,4.40)**		3350	**1.00**	**(0.50,2.20)**	
	Yes	187	**0.10**	**(0.10,0.86)**	***<0.001***	**1.72**	**(0.86,3.68)**	***0.004***	**3.31**	**(2.06,5.20)**	***0.009***	177	**1.80**	**(0.90,3.30)**	***<0.001***
Dyslipidemia	No	2350	**0.46**	**(0.10,2.03)**		**1.19**	**(0.52,3.15)**		**2.70**	**(1.66,4.26)**		2393	**0.90**	**(0.50,2.00)**	
	Yes	1128	**0.39**	**(0.10,1.74)**	***0.036***	**1.45**	**(0.66,3.40)**	***0.001***	**3.01**	**(1.90,4.79)**	***<0.001***	1134	**1.40**	**(0.70,2.70)**	***<0.001***
Hypertension	No	2432	**0.49**	**(0.10,2.04)**		**1.20**	**(0.50,3.17)**		**2.66**	**(1.68,4.27)**		2490	**0.90**	**(0.50,1.90)**	
	Yes	640	**0.32**	**(0.10,1.69)**	***<0.001***	**1.52**	**(0.68,3.45)**	***<0.001***	**3.11**	**(1.95,4.90)**	***<0.001***	1037	**1.50**	**(0.80,3.00)**	***<0.001***

Key: [a] Wilcoxon Mann-Whitney test; [b] Spearman coefficient correlation; **TNF-α** = Tumor Necrosis Factor-α; **hsCRP** = high sensitivity C-Reactive Protein; **IQR** = interquartile range; **SES** = socio-economic status; **MDD** = major depressive disorder; **CVRF** = cardiovascular risk factor.

Table 1: Sample characteristics (n=3'719)

Variables	PsyCoLaus sample						*p*
	Overall		Men		Women		
Demographic							
n (%)	3'719		1'749	(47.03)	1'970	(52.97)	--
Age, mean (SD)	50.93	(8.78)	50.51	(8.78)	51.31	(8.77)	0.006
SES, mean (SD)	3.38	(1.28)	3.54	(1.25)	3.23	(1.28)	<.0001
Lifetime psychiatric disorders, n (%)							
Bipolar disorder	69	(1.86)	36	(2.06)	33	(1.68)	0.39
Dysthymia	81	(2.18)	37	(2.12)	44	(2.23)	0.81
MDD	1624	(43.67)	563	(32.19)	1061	(53.86)	<.0001
Combined MDD	219	(5.89)	60	(3.43)	159	(8.07)	<.0001
Atypical MDD	235	(6.32)	69	(3.95)	166	(8.43)	<.0001
Melancholic MDD	449	(12.07)	152	(8.69)	297	(15.08)	<.0001
Unspecified MDD	721	(19.39)	282	(16.12)	439	(22.28)	<.0001
Anxiety disorders	660	(17.85)	225	(12.95)	435	(22.19)	<.0001
SUD	573	(15.47)	428	(24.57)	145	(7.39)	<.0001
Without diagnoses	1466	(39.42)	799	(45.68)	667	(33.86)	<.0001
Current psychiatric disorders, n (%)							
Bipolar disorder	2	(0.05)	1	(0.06)	1	(0.05)	0.93
Dysthymia	20	(0.54)	6	(0.34)	14	(0.71)	0.13
MDD	660	(17.75)	235	(13.44)	425	(21.57)	<.0001
Combined MDD	106	(2.85)	29	(1.66)	77	(3.91)	<.0001
Atypical MDD	98	(2.64)	31	(1.77)	67	(3.40)	0.002
Melancholic MDD	198	(5.32)	66	(3.77)	132	(6.70)	<.0001
Unspecified MDD	258	(6.94)	109	(6.23)	149	(7.56)	0.11
Anxiety disorders	370	(9.95)	118	(6.75)	252	(12.79)	<.0001
SUD	229	(6.16)	174	(9.95)	55	(2.79)	<.0001
Without diagnoses	3059	(82.25)	1514	(86.56)	1545	(78.43)	<.0001
Inflammatory markers, median (IQR)							
IL-1β [pg/ml]	0.44	(0.10-1.94)	0.39	(0.10-1.73)	0.49	(0.10-2.00)	0.05
IL-6 [pg/ml]	1.28	(0.56-3.27)	1.42	(0.63-3.50)	1.19	(0.49-3.12)	<.001
TNF-α [pg/ml]	2.79	(1.75-4.45)	2.92	(1.86-4.58)	2.64	(1.63-4.26)	<.0001
hsCRP [mg/l]	1.10	(0.50-2.30)	1.00	(0.50-2.10)	1.10	(0.50-2.40)	0.49

Key: SD = standard deviation; **SES** = socio-economic status. A value of 3 represents an SES of III (middle class) on the Hollingshead Scale; **MDD** = major depressive disorder; **SUD** = substance use disorders; **IQR** = Inter-quartile range (the 25% and 75% quartiles are provided); **IL-1β** = Interleukin-1β; **IL-6** = Interleukin-6; **TNF-α** = Tumor Necrosis Factor-α; **hsCRP** = high sensitivity C-reactive protein; Median and IQR of inflammatory markers were not logarithmically transformed (n Il-1β, IL-6, TNF-α=3478, 1640 men/1838 women; n hsCRP=3527, 1684 men/1843 women).

Table 2: Associations between lifetime and current disorders and pro-inflammatory proteins

	Interleukin-1β [pg/l][a]			Interleukin-6 [pg/ml][b]			TNF-α [pg/ml][b]			hsCRP [mg/l][b]		
	OR	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
Lifetime diagnoses												
Bipolar	0.82	(0.49,1.36)	*0.443*	[c]--	--	--	-0.19	(-0.42,0.05)	*0.119*	**0.33**	**(0.09,0.56)**	***0.008***
Dysthymia	0.82	(0.51,1.31)	*0.401*	-0.13	(-0.50,0.24)	*0.478*	0.00	(-0.21,0.22)	*0.984*	-0.09	(-0.31,0.13)	*0.421*
MDD	0.91	(0.79,1.05)	*0.194*	-0.07	(-0.18,0.04)	*0.186*	-0.04	(-0.10,0.02)	*0.207*	-0.02	(-0.09,0.04)	*0.494*
Combined MDD	0.90	(0.68,1.20)	*0.484*	-0.08	(-0.30,0.15)	*0.510*	-0.07	(-0.20,0.06)	*0.290*	-0.01	(-0.15,0.13)	*0.910*
Atypical MDD	0.90	(0.68,1.19)	*0.463*	0.16	(-0.06,0.38)	*0.158*	0.11	(-0.02,0.24)	*0.100*	**0.14**	**(0.01,0.28)**	***0.038***
Melancholic MDD	0.99	(0.81,1.22)	*0.918*	-0.04	(-0.21,0.12)	*0.606*	-0.01	(-0.11,0.08)	*0.785*	-0.04	(-0.14,0.06)	*0.407*
Unspecified MDD	0.95	(0.80,1.12)	*0.520*	-0.12	(-0.25,0.02)	*0.094*	-0.07	(-0.15,0.01)	*0.088*	-0.06	(-0.14,0.03)	*0.178*
Anxiety disorders any	0.88	(0.74,1.05)	*0.156*	-0.08	(-0.22,0.06)	*0.270*	0.00	(-0.08,0.08)	*0.958*	**-0.11**	**(-0.19,-0.02)**	***0.013***
Substance use disorders	0.99	(0.82,1.20)	*0.900*	0.11	(-0.04,0.26)	*0.141*	0.06	(-0.03,0.15)	*0.180*	[c]--	--	--
Others	1.12	(0.98,1.29)	*0.109*	0.05	(-0.06,0.16)	*0.337*	0.04	(-0.02,0.10)	*0.207*	0.02	(-0.05,0.08)	*0.611*
Current diagnoses												
Bipolar	--	--	--	--	--	--	--	--	--	--	--	--
Dysthymia	0.83	(0.34,2.02)	*0.688*	0.51	(-0.19,1.21)	*0.157*	0.15	(-0.25,0.56)	*0.458*	0.03	(-0.41,0.47)	*0.894*
MDD	1.01	(0.85,1.20)	*0.891*	0.10	(-0.04,0.24)	*0.151*	0.01	(-0.07,0.09)	*0.877*	-0.08	(-0.17,0.01)	*0.067*
Combined MDD	0.80	(0.53,1.19)	*0.262*	-0.13	(-0.44,0.19)	*0.425*	-0.07	(-0.25,0.12)	*0.483*	-0.04	(-0.23,0.16)	*0.708*
Atypical MDD	0.93	(0.62,1.39)	*0.715*	0.27	(-0.05,0.59)	*0.101*	0.07	(-0.12,0.26)	*0.459*	0.19	(-0.01,0.40)	*0.063*
Melancholic MDD	1.17	(0.87,1.57)	*0.292*	0.10	(-0.14,0.33)	*0.418*	0.05	(-0.09,0.18)	*0.508*	-0.14	(-0.28,0.00)	*0.056*
Unspecified MDD	1.03	(0.80,1.34)	*0.811*	0.09	(-0.11,0.30)	*0.366*	-0.02	(-0.14,0.10)	*0.716*	-0.13	(-0.25,0.00)	*0.050*
Anxiety disorders any	0.94	(0.75,1.17)	*0.574*	-0.12	(-0.29,0.06)	*0.197*	0.00	(-0.10,0.10)	*1.000*	**-0.13**	**(-0.24,-0.03)**	***0.015***
Substance use disorders	0.93	(0.71,1.23)	*0.630*	0.19	(-0.03,0.41)	*0.093*	0.07	(-0.05,0.20)	*0.254*	0.12	(-0.01,0.26)	*0.074*
Others	0.99	(0.83,1.18)	*0.891*	-0.10	(-0.24,0.04)	*0.151*	-0.01	(-0.09,0.07)	*0.877*	0.08	(-0.01,0.17)	*0.067*

Key: [a] logistic regression with Intreleukin-1 beta concentration dichotomized at the median (n=3478); [b] multiple regression with logarithmically transformed cytokine (n=3478) or CRP concentrations (n=3527); [c] results not reported here because of a gender interaction; **TNF-α** = Tumor Necrosis Factor-α; **hsCRP** = High sensitivity C-Reactive Protein; **OR** = odds ratio; **CI** = confidence interval; **MDD** = major depressive disorder;

Associations between pro-inflammatory markers and a current diagnosis of bipolar disorder could not be assessed due to small sample size;
A model for each mental disorder was run separately adjusting for socio-demographic variables (age, gender and socio-economic status).

Table 3: Associations between lifetime mental disorders and pro-inflammatory proteins

	Interleukin-1β [pg/l] **OR[a]** **95% CI** ***p***				**Interleukin-6 [pg/ml]** **β[b]** **95% CI** ***p***				**Tumor Necrosis Factor-α [pg/ml]** **β[b]** **95% CI** ***p***				**hsC-Reactive Protein [mg/l]** **β[b]** **95% CI** ***p***			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
AIC	4811	4817	4819	4816	12642	12640	12622	12605	9363	9364	9357	9348	9853	9858	9808	9250
Lifetime diagnoses																
BPD	0.80	0.75	0.75	0.75	[c]--	--	--	--	-0.22	**-0.27**	**-0.28**	**-0.29**	**0.34**	**0.32**	**0.31**	0.22
	(0.48,1.34)	(0.43,1.30)	(0.43,1.30)	(0.43,1.30)	--	--	--	--	(-0.45,0.02)	**(-0.52,-0.01)**	**(-0.53,-0.03)**	**(-0.54,-0.04)**	**(0.09,0.58)**	**(0.07,0.58)**	**(0.06,0.57)**	(-0.01,0.46)
	0.396	*0.298*	*0.308*	*0.302*	--	--	--	--	*0.069*	***0.038***	***0.030***	***0.023***	***0.006***	***0.014***	***0.016***	*0.064*
Dysth	0.78	0.78	0.78	0.77	-0.19	-0.20	-0.21	-0.20	-0.03	-0.04	-0.04	-0.04	-0.09	-0.10	-0.10	-0.04
	(0.48,1.24)	(0.48,1.24)	(0.49,1.25)	(0.48,1.24)	(-0.56,0.18)	(-0.58,0.17)	(-0.59,0.16)	(-0.57,0.17)	(-0.24,0.19)	(-0.25,0.18)	(-0.26,0.17)	(-0.25,0.18)	(-0.32,0.13)	(-0.32,0.12)	(-0.32,0.12)	(-0.25,0.16)
	0.291	*0.291*	*0.296*	*0.282*	*0.313*	*0.282*	*0.256*	*0.287*	*0.795*	*0.743*	*0.711*	*0.741*	*0.403*	*0.385*	*0.359*	*0.679*
Comb MDD	0.87	0.86	0.86	0.87	-0.13	-0.22	-0.24	**-0.27**	-0.10	-0.14	**-0.15**	**-0.16**	0.00	-0.02	-0.03	-0.08
	(0.65,1.17)	(0.63,1.17)	(0.64,1.18)	(0.64,1.19)	(-0.36,0.11)	(-0.46,0.02)	(-0.48,0.01)	**(-0.51,-0.02)**	(-0.24,0.04)	(-0.28,0.00)	**(-0.29,-0.01)**	**(-0.30,-0.01)**	(-0.14,0.15)	(-0.17,0.13)	(-0.18,0.12)	(-0.22,0.05)
	0.352	*0.335*	*0.352*	*0.378*	*0.291*	*0.078*	*0.056*	***0.031***	*0.150*	*0.053*	***0.042***	***0.031***	*0.963*	*0.816*	*0.695*	*0.236*
Atyp MDD	0.86	0.85	0.86	0.88	0.10	0.03	0.03	-0.02	0.07	0.04	0.04	0.03	0.14	0.13	0.10	0.00
	(0.65,1.15)	(0.64,1.14)	(0.64,1.15)	(0.66,1.18)	(-0.13,0.32)	(-0.20,0.26)	(-0.21,0.26)	(-0.25,0.21)	(-0.06,0.20)	(-0.09,0.18)	(-0.09,0.18)	(-0.11,0.16)	(0.00,0.28)	(-0.02,0.27)	(-0.04,0.24)	(-0.14,0.13)
	0.308	*0.287*	*0.304*	*0.395*	*0.410*	*0.787*	*0.829*	*0.888*	*0.295*	*0.513*	*0.529*	*0.700*	*0.052*	*0.083*	*0.151*	*0.942*
Mela MDD	0.94	0.93	0.93	0.93	-0.10	-0.17	-0.17	-0.16	-0.04	-0.08	-0.08	-0.07	-0.03	-0.05	-0.05	-0.01
	(0.76,1.17)	(0.74,1.17)	(0.74,1.17)	(0.74,1.17)	(-0.27,0.08)	(-0.35,0.01)	(-0.35,0.01)	(-0.34,0.02)	(-0.14,0.06)	(-0.18,0.03)	(-0.18,0.03)	(-0.17,0.04)	(-0.14,0.07)	(-0.16,0.06)	(-0.16,0.06)	(-0.11,0.10)
	0.600	*0.536*	*0.534*	*0.508*	*0.279*	*0.062*	*0.061*	*0.089*	*0.382*	*0.158*	*0.158*	*0.193*	*0.542*	*0.397*	*0.416*	*0.901*
Unsp MDD	0.91	0.90	0.91	0.91	**-0.15**	**-0.19**	**-0.20**	**-0.19**	**-0.09**	**-0.10**	**-0.11**	**-0.10**	-0.04	-0.05	-0.06	-0.04
	(0.76,1.09)	(0.75,1.09)	(0.76,1.09)	(0.75,1.09)	**(-0.29,-0.01)**	**(-0.33,-0.04)**	**(-0.35,-0.06)**	**(-0.34,-0.05)**	**(-0.17,0.00)**	**(-0.19,-0.02)**	**(-0.19,-0.02)**	**(-0.19,-0.02)**	(-0.13,0.04)	(-0.14,0.04)	(-0.15,0.03)	(-0.12,0.04)
	0.302	*0.286*	*0.304*	*0.290*	***0.042***	***0.012***	***0.007***	***0.009***	***0.044***	***0.018***	***0.013***	***0.016***	*0.333*	*0.254*	*0.179*	*0.371*
ADA	0.90	0.90	0.90	0.90	-0.06	-0.07	-0.08	-0.06	0.01	0.00	0.00	0.01	**-0.12**	**-0.12**	**-0.13**	-0.08
	(0.75,1.07)	(0.75,1.07)	(0.75,1.08)	(0.75,1.08)	(-0.20,0.08)	(-0.21,0.07)	(-0.22,0.06)	(-0.20,0.08)	(-0.07,0.09)	(-0.08,0.08)	(-0.08,0.08)	(-0.08,0.09)	**(-0.20,-0.03)**	**(-0.21,-0.04)**	**(-0.21,-0.04)**	(-0.16,0.00)
	0.243	*0.241*	*0.248*	*0.244*	*0.423*	*0.311*	*0.261*	*0.377*	*0.800*	*0.963*	*0.978*	*0.879*	***0.007***	***0.005***	***0.003***	*0.053*
SUD	1.01	1.01	1.03	1.04	0.14	0.13	0.05	0.06	0.07	0.07	0.03	0.04	[c]--	--	--	--
	(0.83,1.22)	(0.83,1.22)	(0.85,1.25)	(0.85,1.27)	(-0.01,0.29)	(-0.03,0.28)	(-0.11,0.20)	(-0.09,0.22)	(-0.02,0.16)	(-0.02,0.15)	(-0.06,0.12)	(-0.05,0.13)	--	--	--	--
	0.944	*0.960*	*0.779*	*0.701*	*0.076*	*0.106*	*0.544*	*0.432*	*0.114*	*0.147*	*0.456*	*0.374*	--	--	--	--

Key: [a] logistic regression with Intreleukin-1 beta concentration dichotomized at the median (n=3478); [b] multiple regression with logarithmically transformed cytokine (n=3478) or CRP concentrations (n=3527); [c] results not reported here because of a gender interaction; **OR** = odds ratio; **CI** = confidence interval; **AIC** = Akaike information criterion; **BPD** = bipolar disorder; **Dysth** = dysthymia; **MDD** = major depressive disorder; **Comb MDD** = combined MDD; **Atyp MDD** = atypical MDD; **Mela MDD** = melancholic MDD; **Unsp MDD** = unspecified MDD; **ADA** = anxiety disorders any; **SUD** = substance use disorders;
Model 1: all mental disorders simultaneously entered into the models adjusted for socio-demographic characteristics (age, sex, socio-economic status);
Model 2: Model 1 and further adjusted for psychotropic medication (antidepressants, mood stabilizers and antipsychotics);

Model 3: Model 2 and further adjusted for behavioral cardiovascular risk factors (physical inactivity and smoking);
Model 4: Model 3 and further adjusted for physical cardiovascular risk factors (BMI, diabetes, hypertension, dyslipidemia);
The lower the AIC values, the better the goodness of fit.

Table 4: Associations between current mental disorders and pro-inflammatory proteins

	Interleukin-1β [pg/l] **OR[a]** **95% CI** ***p***				**Interleukin-6 [pg/ml]** **β[b]** **95% CI** ***p***				**Tumor Necrosis Factor-α [pg/ml]** **β[b]** **95% CI** ***p***				**hsC-Reactive Protein [mg/l]** **β[b]** **95% CI** ***p***			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
AIC	4812	4817	4820	4816	12641	12644	12627	12609	9369	9373	9367	9357	9856	9859	9807	9246
Current diagnoses																
Dysth	0.83	0.83	0.85	0.81	0.53	0.53	0.49	0.49	0.16	0.16	0.15	0.15	0.07	0.07	0.03	0.01
	(0.34,2.01)	(0.34,2.02)	(0.35,2.05)	(0.33,1.96)	(-0.17,1.23)	(-0.17,1.23)	(-0.21,1.19)	(-0.20,1.19)	(-0.25,0.57)	(-0.25,0.57)	(-0.26,0.55)	(-0.26,0.55)	(-0.37,0.51)	(-0.37,0.52)	(-0.41,0.46)	(-0.40,0.41)
	0.680	*0.681*	*0.709*	*0.636*	*0.135*	*0.138*	*0.168*	*0.166*	*0.439*	*0.437*	*0.475*	*0.473*	*0.752*	*0.740*	*0.908*	*0.963*
Comb MDD	0.81	0.82	0.83	0.84	-0.09	-0.14	-0.15	-0.20	-0.06	-0.08	-0.09	-0.10	-0.04	-0.07	-0.10	**-0.20**
	(0.54,1.21)	(0.55,1.24)	(0.55,1.25)	(0.56,1.26)	(-0.41,0.22)	(-0.46,0.18)	(-0.47,0.17)	(-0.52,0.12)	(-0.25,0.12)	(-0.27,0.11)	(-0.27,0.10)	(-0.29,0.09)	(-0.24,0.16)	(-0.27,0.13)	(-0.30,0.10)	**(-0.39,-0.02)**
	0.303	*0.352*	*0.373*	*0.397*	*0.572*	*0.391*	*0.348*	*0.218*	*0.504*	*0.391*	*0.369*	*0.299*	*0.688*	*0.504*	*0.331*	***0.032***
Atyp MDD	0.94	0.95	0.95	0.98	0.30	0.27	0.27	0.23	0.07	0.06	0.06	0.04	0.19	0.17	0.17	0.03
	(0.62,1.42)	(0.63,1.44)	(0.63,1.44)	(0.65,1.48)	(-0.02,0.63)	(-0.06,0.59)	(-0.05,0.60)	(-0.10,0.55)	(-0.12,0.26)	(-0.13,0.25)	(-0.13,0.25)	(-0.15,0.23)	(-0.02,0.39)	(-0.04,0.38)	(-0.04,0.37)	(-0.16,0.22)
	0.763	*0.807*	*0.807*	*0.920*	*0.069*	*0.110*	*0.100*	*0.175*	*0.468*	*0.549*	*0.524*	*0.647*	*0.075*	*0.106*	*0.116*	*0.736*
Mela MDD	1.17	1.18	1.18	1.18	0.12	0.08	0.09	0.12	0.04	0.03	0.03	0.04	-0.14	**-0.16**	**-0.15**	-0.09
	(0.87,1.57)	(0.87,1.61)	(0.87,1.60)	(0.87,1.60)	(-0.11,0.36)	(-0.16,0.32)	(-0.15,0.33)	(-0.12,0.35)	(-0.09,0.18)	(-0.11,0.17)	(-0.11,0.17)	(-0.10,0.18)	(-0.28,0.01)	**(-0.31,-0.01)**	**(-0.30,0.00)**	(-0.23,0.05)
	0.302	*0.277*	*0.286*	*0.286*	*0.307*	*0.510*	*0.451*	*0.347*	*0.523*	*0.676*	*0.628*	*0.549*	*0.064*	***0.034***	***0.044***	*0.201*
Unsp MDD	1.04	1.04	1.05	1.05	0.10	0.09	0.08	0.08	-0.02	-0.03	-0.03	-0.03	**-0.13**	**-0.14**	**-0.15**	**-0.12**
	(0.80,1.35)	(0.80,1.36)	(0.81,1.36)	(0.81,1.37)	(-0.10,0.31)	(-0.12,0.30)	(-0.13,0.29)	(-0.12,0.29)	(-0.14,0.10)	(-0.15,0.09)	(-0.15,0.09)	(-0.15,0.09)	**(-0.26,0.00)**	**(-0.27,-0.01)**	**(-0.28,-0.02)**	**(-0.24,-0.01)**
	0.774	*0.749*	*0.724*	*0.695*	*0.319*	*0.394*	*0.444*	*0.419*	*0.712*	*0.657*	*0.618*	*0.672*	***0.046***	***0.036***	***0.022***	***0.040***
ADA	0.94	0.95	0.95	0.95	-0.15	-0.15	-0.16	-0.14	-0.01	-0.01	-0.02	-0.01	**-0.14**	**-0.14**	**-0.15**	-0.07
	(0.75,1.18)	(0.76,1.19)	(0.76,1.19)	(0.76,1.19)	(-0.32,0.03)	(-0.33,0.03)	(-0.34,0.01)	(-0.32,0.04)	(-0.11,0.10)	(-0.12,0.09)	(-0.12,0.09)	(-0.11,0.10)	**(-0.24,-0.03)**	**(-0.25,-0.03)**	**(-0.25,-0.04)**	(-0.18,0.03)
	0.606	*0.630*	*0.642*	*0.654*	*0.109*	*0.093*	*0.070*	*0.122*	*0.906*	*0.823*	*0.753*	*0.920*	***0.015***	***0.011***	***0.009***	*0.148*
SUD	0.94	0.94	0.96	0.97	0.19	0.18	0.12	0.14	0.08	0.07	0.04	0.05	0.14	0.13	0.08	0.11
	(0.71,1.24)	(0.71,1.25)	(0.72,1.27)	(0.73,1.28)	(-0.03,0.41)	(-0.04,0.40)	(-0.10,0.34)	(-0.08,0.36)	(-0.05,0.20)	(-0.06,0.20)	(-0.08,0.17)	(-0.08,0.18)	(0.00,0.27)	(-0.01,0.26)	(-0.06,0.21)	(-0.01,0.24)
	0.653	*0.671*	*0.775*	*0.805*	*0.084*	*0.100*	*0.296*	*0.225*	*0.241*	*0.272*	*0.502*	*0.438*	*0.052*	*0.068*	*0.270*	*0.077*

Key: [a] logistic regression with Intreleukin-1 beta concentration dichotomized at the median (n=3478); [b] multiple regression with logarithmically transformed cytokine (n=3478) or CRP concentrations (n=3527);
OR = odds ratio; **CI** = confidence interval; **AIC** = Akaike information criterion; **Dysth** = dysthymia; **MDD** = major depressive disorder; **Comb MDD** = combined MDD; **Atyp MDD** = atypical MDD; **Mela MDD** = melancholic MDD; **Unsp MDD** = unspecified MDD; **ADA** = anxiety disorders any; **SUD** = substance use disorders;
Model 1: all mental disorders simultaneously entered into the models and adjusted for socio-demographic characteristics (age, sex, socio-economic status);
Model 2: Model 1 and further adjusted for psychotropic medication (antidepressants, mood stabilizers and antipsychotics);
Model 3: Model 2 and further adjusted for behavioral cardiovascular risk factors (physical inactivity and smoking);
Model 4: Model 3 and further adjusted for physical cardiovascular risk factors (BMI, diabetes, hypertension, dyslipidemia);
Current diagnosis of bipolar disorder not assessed due to small sample size;
The lower the AIC values, the better the goodness of fit.