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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 3719 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 ($\beta = 0.13$ (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 ($\beta = -0.27$ (−0.51,−0.02); $\beta = -0.19$ (−0.34,−0.05), respectively) and TNF-α ($\beta = -0.16$ (−0.30,−0.01); $\beta = -0.10$ (−0.19,−0.02), respectively), whereas current combined and unspecified depression were associated with decreased levels of hsCRP ($\beta = -0.20$ (−0.39,−0.02); $\beta = -0.12$ (−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.

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.,

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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 and 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 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 6736 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 35–66 years ($N = 5535$) agreed to take part in the psychiatric evaluation (PsyCoLaus), which resulted in a sample of 3719 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 3719 participants, 3527 had measures of high-sensitivity CRP (hsCRP) and 3478 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 and 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.