



Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: Findings from the Netherlands Study of Depression and Anxiety (NESDA)

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Cohort study

Summary

Objective: Depression and anxiety have been suggested to be associated with systemic inflammation upregulation. However, results are not always consistent, which may be due to symptom heterogeneity of depression and anxiety. There are some indications that associations with inflammation are mainly driven by somatic symptoms of depression and anxiety. We therefore set out to evaluate the differential association of somatic and cognitive symptoms of depression and anxiety with inflammation, while adjusting for demographic, health related, and lifestyle related variables.

Methods: We evaluated baseline data from 2861 participants from the Netherlands Study of Depression and Anxiety (NESDA). The Inventory of Depressive Symptomatology and the Beck Anxiety Inventory were used to assess depressive symptoms and anxiety symptoms. For both scales somatic and cognitive symptoms scales were calculated. Baseline blood samples were collected to determine high sensitivity C-Reactive Protein (CRP), interleukin (IL)-6, and Tumor Necrosis Factor (TNF)- α . We used linear regression to analyze the associations adjusting for demographics and health indicators and markers for an unhealthy lifestyle.

Results: After adjustment for sociodemographic and health indicators, depressive symptoms were associated with higher levels of CRP, IL-6 and TNF- α . This association was mainly driven by somatic symptoms. For anxiety, somatic symptoms were associated with higher levels of CRP, IL-6

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and TNF- α , whereas cognitive anxiety symptoms were associated with CRP (men only). Markers of an unhealthy lifestyle explained the significant associations.

Conclusions: Especially somatic symptoms of depression and anxiety are associated with inflammation. However, this association was mostly mediated through unhealthy lifestyles among depressed and anxious individuals.

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1. Introduction

Depression and anxiety have been found to be prognostically associated with various somatic conditions, including cardiac disease (van Melle et al., 2004; Meijer et al., 2011), diabetes (Stuart and Baune, 2012) and obesity (Luppino et al., 2010). Low grade inflammation has been proposed as one of the physiological links between both depression and anxiety and adverse somatic outcomes (Howren et al., 2009; Stuart and Baune, 2012). In the last decade a substantial amount of research has been published on the depression–inflammation relationship, in healthy (Dowlati et al., 2010) and cardiac populations (Howren et al., 2009). Most of these studies concern cross-sectional research, although some prospective studies have been published (Gimeno et al., 2009; Stewart et al., 2009; Duivis et al., 2011; Shaffer et al., 2011).

Despite the substantial amount of research published on the depression–inflammation link, results are still conflicting (Howren et al., 2009), with some studies reporting positive associations (Bankier et al., 2009; Pizzi et al., 2010) and others reporting negative findings (Whooley et al., 2007; McGlory, 2009). Stewart et al. (2009) found that depressive symptoms predicted an upregulation of interleukin 6 (IL-6) after a 6-year follow-up in an otherwise healthy sample, but inflammation did not predict depressive symptoms after 6 years. Another study reported that recurrent depressive symptoms were associated with subsequent inflammation, although this association was largely explained by lifestyle behaviors (Duivis et al., 2011). In contrast, Gimeno et al. (2009) found that after 11 years of follow-up, C-Reactive Protein (CRP) and IL-6 were predictive of cognitive symptoms of depression, but not vice versa. It is obvious from the preceding that there is still considerable debate on whether or not depression and inflammation are associated and which factors contribute to this relationship. Meta-analyses (Howren et al., 2009; Dowlati et al., 2010) have also suggested that substantial heterogeneity exists between studies which could be attributed to the differences in the study samples studied or the questionnaires used to determine depressive symptoms.

Another possible explanation for inconsistencies in the depression and inflammation link could be that most studies report only on depression as a whole, whereas it might be more suitable to pay attention to individual depressive symptoms or dimension scores in relation to inflammation (Elovainio et al., 2009). Based on the sickness behavior theory (Dantzer et al., 2008), which argues that somatic depressive-like symptoms such as fatigue, sleeping problems, anorexia, and motor slowing can be the result of upregulated inflammation levels, one could expect that possible associations between depression and inflammation are being missed when taking depression as a whole into account. It could thus be hypothesized that somatic symptoms show a stronger

association with inflammation than cognitive symptoms, and this should be taken into account when investigating the depression–inflammation relationship.

In the case of anxiety, less research is conducted on the associations with inflammation. However, there is some evidence suggesting that anxiety is associated with inflammation (Bankier et al., 2008; Hoge et al., 2009; von Kanel et al., 2010) reporting small to large effect sizes. However, these studies included relatively small samples ($N < 120$), which could mask true effect sizes. As with depression, anxiety also consists of somatic and cognitive symptoms. Although no study has investigated the association of somatic and cognitive anxiety symptoms with inflammation, one study found that in women somatic symptoms of anxiety were associated with an increased CHD risk, whereas more psychological symptoms of anxiety were not (Nabi et al., 2010).

An additional possible explanation for prior conflicting results of studies examining the link between anxiety/depression and inflammation could be the possible mediating effects of for instance lifestyle behaviors such as smoking, physical activity, alcohol consumption and overweight. These factors are not always included in multivariable analyses, even though there is considerable evidence that markers of an unhealthy lifestyle are associated with both depressive (Wiesbeck et al., 2008; Patten et al., 2009; Luppino et al., 2010) and anxiety symptoms (Mykletun et al., 2008; Strine et al., 2008) as well as inflammation (Eckel et al., 2005; Reichert et al., 2009; Dod et al., 2010). For instance, the meta-analysis by Howren et al. (2009) found that effect sizes were considerably smaller in studies that adjusted for body mass index (BMI). Furthermore, a meta-analysis on depression and overweight reported that obesity can be the result of depression, but also vice versa. Obesity has also been found to be associated with higher levels of inflammation (O'Connor et al., 2009). Finally, as the majority of studies has a rather small sample size ($N < 100$), reported effect sizes can be masked. In order to detect true significant associations and to be able to adjust for important confounders or mediators, large sample sizes are needed.

We previously found in a large sample of 2415 participants that depression diagnosis was associated with immune dysregulation in men with a late onset depression (Vogelzangs et al., 2012), but we did not distinguish in symptom dimensions of depression. We therefore set out to conduct secondary data-analysis in this same sample in which we will thoroughly investigate the relationship between symptoms profiles of depression and anxiety with inflammation. We hypothesize that (1) mainly the somatic symptoms of depression and anxiety are associated with inflammation, and (2) that the association between (somatic) depressive and anxiety symptoms and inflammation will be partly explained by markers of an unhealthy lifestyle such as smoking, alcohol intake, BMI and physical inactivity.

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