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# Does tryptophan degradation along the kynurenine pathway mediate the association between pro-inflammatory immune activity and depressive symptoms?

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**Summary**
*Background:* Several studies have suggested that induced tryptophan (TRP) degradation through the kynurenine (KYN) pathway by the enzyme indoleamine 2,3-dioxygenase (IDO) is implicated in the relation between depression and inflammation. We investigated the role of tryptophan degradation in the relationship between inflammatory markers and depressive symptoms in the Netherlands Study of Depression and Anxiety (NESDA) and hypothesized that tryptophan degradation would mediate (part of) this association.
*Methods:* 2812 Participants of NESDA were included in this study including 1042 persons with current major depressive disorder (MDD). Assessments of C-reactive protein (CRP), interleukin (IL)-6, tumor-necrosis factor (TNF)-$\alpha$, KYN and TRP were obtained from fasting blood samples at the baseline assessment. Tryptophan degradation was estimated by calculating the ratio [KYN/TRP]. Depressive symptoms were measured with the Inventory of Depressive Symptomatology.
*Results:* Significant associations between inflammation and depressive symptoms were found for CRP and IL-6, for the total group and the subgroup of patients with current MDD. Adjustment for KYN/TRP did not attenuate these associations. There were no significant indirect effects for CRP

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on depressive symptoms mediated by KYN/TRP for the whole group ($B = -0.032$; 95% CI: −0.103 to 0.028) and for the subgroup of patients with current MDD ($B = 0.059$; 95% CI: −0.037 to 0.165). Also IL-6 did not indirectly affect depressive symptoms through KYN/TRP in the total group ($B = -0.023$; 95% CI: −0.093 to 0.045) and in the MDD subgroup $B = 0.052$; 95% CI: −0.019 to 0.144). Finally, no significant relation between depressive symptoms and KYN/TRP was found in the whole group ($\beta = -0.019$, $p = 0.311$) nor in the subgroup with MDD ($\beta = 0.025$, $p = 0.424$).
*Conclusions:* We did not find indications for tryptophan degradation, measured by KYN/TRP, to mediate the relationship between inflammation and depressive symptoms.


## Introduction

There is considerable evidence that inflammation and depression are associated. Two recent meta-analyses showed that inflammation markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α are associated with depression (Dowlati et al., 2010; Howren et al., 2009), although the associations are not very strong. Also in medically ill patients an association has been established, for example in patients with coronary heart disease (Howren et al., 2009). Furthermore, proinflammatory cytokine treatment in medically ill patients leads to an increased onset of major depression (Raison et al., 2006). These findings strengthen the theory that depression is — at least partly — a result of an activated immune system (Leonard, 2010; Maes et al., 2009)

One of the suggested mechanisms linking inflammation and depression is the enzyme indoleamine 2,3-dioxygenase (IDO). IDO is activated by proinflammatory cytokines and catalyzes the rate-limiting step in the degradation of the essential amino acid tryptophan (TRP) through the kynurenine (KYN) pathway, resulting in a reduced availability of tryptophan for the synthesis of serotonin and the formation of KYN and its related neuroactive kynurenine pathway metabolites (Fig. 1). Tryptophan is also degraded to kynurenine by the liver enzyme tryptophan 2,3-dioxygenase (TDO) in non-inflammatory states. According to the serotonin hypothesis of depression, diminished activity of the serotonin system can lead to depressive symptoms (Lapin and Oxenkrug, 1969). Furthermore, the neurotoxic metabolites of KYN 3-hydroxykynurenine (3-OH-KYN) and quinolinic acid (QA) are also implicated in the development of depressive symptoms (Dantzer et al., 2011). All these features make IDO a candidate linking inflammation and depression. Many commentaries, reviews and expert opinions on the development of depression mention the potential role of IDO and tryptophan degradation (Chopra et al., 2011; Christmas et al., 2011; Dantzer et al., 2011; Leonard, 2010; Maes et al., 2011; Sublette and Postolache, 2012), but to date, most of the evidence on the role of IDO was based on animal studies (e.g., (O'Connor et al., 2009a,c)) or on human studies in which depression was artificially induced by pro-inflammatory IFN-α therapy (Capuron et al., 2003; Wichers et al., 2005). A first population based study in healthy young adults showed that IDO-activity was associated with depressive symptoms (Elovainio et al., 2012). However as far as we know, no previous study has assessed a large group of depressed subjects or actually examined whether IDO-activity mediates the association between inflammatory markers and depressive symptoms.

In this paper we present the results of a study investigating the role of tryptophan degradation via the kynurenine pathway in the relationship between inflammatory markers and depressive symptoms in the Netherlands Study of Depression and Anxiety (NESDA), a cohort consisting of almost 3000 subjects of whom the majority was diagnosed with a current or remitted depressive or anxiety disorder. In this cohort an association between inflammatory markers and depressive disorder was established earlier (Vogelzangs et al., 2012). We used the ratio between the substrate and product of IDO and TDO (i.e., KYN/TRP) as an indication of tryptophan degradation and thus IDO and TDO activity. KYN/TRP is used in most studies investigating IDO activity. We hypothesized a priori that KYN/TRP would mediate (part of) the association between inflammatory markers and depressive symptoms, both in the total sample and in a subgroup of participants diagnosed with current major depressive disorder (MDD).

## Methods and materials

### Subjects and design

Subjects participating in the present study were enrolled in NESDA, an ongoing longitudinal cohort study conducted among 2981 adult subjects (age 18–65 years). The aim of NESDA is to examine the long-term course of depression and anxiety disorders. The rationale, methods, and recruitment strategy have been described elsewhere (Penninx et al., 2008). The NESDA sample consists of a total of 2981 subjects and includes patients with a current diagnosis of depression and/or anxiety disorder, subjects with a life-time, but no current diagnosis or at risk because of a family history or sub threshold depressive or anxiety symptoms, and healthy controls. To represent various settings and stages of psychopathology, depressed or anxious subjects were recruited at three different locations in the Netherlands in different settings: community, primary care, and specialized mental healthcare organizations. The research protocol was approved by the Ethical Committee of participating universities, and after complete description of the study all respondents provided written informed consent.

NESDA subjects were assessed between September 2004 and February 2007 during a 4-hour visit to one of the seven