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The association between plasma tryptophan catabolites and depression: The role of symptom profiles and inflammation

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ABSTRACT

Background: Tryptophan catabolites ("TRYCATs") produced by the kynurenine pathway (KP) may play a role in depression pathophysiology. Studies comparing TRYCATs levels in depressed subjects and controls provided mixed findings. We examined the association of TRYCATs levels with 1) the presence of Major Depressive Disorder (MDD), 2) depressive symptom profiles and 3) inflammatory markers.

Methods: The sample from the Netherlands Study of Depression and Anxiety included participants with current (n = 1100) or remitted (n = 753) MDD DSM-IV diagnosis and healthy controls (n = 642). Plasma levels of tryptophan (TRP), kynurenine (KYN), kynurenic acid (KynA), quinolinic acid (QA), C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor (TNF) were measured. Atypical/energy-related symptom (AES), melancholic symptom (MS) and anxious-distress symptom (ADS) profiles were derived from questionnaires.

Results: After adjustment for age, sex, education, smoking status, alcohol consumption and chronic diseases, no significant differences in TRYCATs were found comparing MDD cases versus controls. The MS profile was associated ($q < 0.05$) with lower KynA ($\beta = -0.05$), while AES was associated with higher KYN ($\beta = 0.05$), QA ($\beta = 0.06$) and TRP ($\beta = 0.06$). Inflammatory markers were associated with higher KYN (CRP $\beta = 0.12$, IL-6 $\beta = 0.08$, TNF $\beta = 0.10$) and QA (CRP $\beta = 0.21$, IL-6 $\beta = 0.12$, TNF $\beta = 0.18$). Significant differences against controls emerged after selecting MDD cases with high (top 30%) CRP (KYN d = 0.20, QA d = 0.33) and high TNF (KYN d = 0.24; QA d = 0.39).

Conclusions: TRYCATs levels were related to specific clinical and biological features, such as atypical symptoms or a proinflammatory status. Modulation of KP may potentially benefit a specific subset of depressed patients. Clinical studies should focus on patients with clear evidence of KP dysregulations.

1. Introduction

Dysregulation of the kynurenine pathway (KP) responsible for tryptophan (TRP) metabolism towards bioactive catabolites ("TRYCATs"), is a candidate pathophysiological mechanisms linking inflammation to depression (Savitz, 2020; Cervenka et al., 2017; Haroon et al., 2012). Inflammatory signals such as tumor-necrosis factor (TNF) and interferon-γ activate the enzyme indoleamine-2,3 dioxygenase (IDO), which converts TRP to kynurenine (KYN) (Dantzer, 2017; O'Connor et al., 2009; Robinson et al. Jan, 2005). In the central nervous system, infiltrated macrophages or microglial cells convert KYN in neurotoxic end-products such as quinolinic acid (QA), a glutamate-receptor agonist potentially implicated in neuronal damage in brain areas involved in mood regulation (Latif-Hernandez et al., 2016; Forrest et al., 2015; Savitz et al., 2015). In contrast, kynurenic acid (KynA), another TRYCAT, is generally considered neuroprotective acting as a glutamate-receptor antagonist (Savitz, 2020).

A recent meta-analysis (Marx et al.), summarizing from 9

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(991subjects) to 57 (7252subjects) studies across different TRYCATs, reported that subjects with Major Depressive Disorder (MDD) had lower levels of TRP (ES[effect size] = −0.51), KYN (ES = −0.26) and KynA (ES = −0.37) as compared to healthy controls, but no difference was found for QA (ES = −0.03). However, the overwhelming majority of studies in the meta-analysis was of small size (N < 100) from selected clinical samples and effect estimates were not adjusted for relevant lifestyle and health factors. It is therefore difficult to extrapolate the results to the overall population of MDD patients. Furthermore, substantial statistical heterogeneity was detected in the pooled estimates, likely due to major methodological differences across studies. Nevertheless, as for many other biomarkers, large individual differences in TRYCATs levels may exist within subjects with MDD. Indication of inflammation, a key trigger in the KP, is indeed present in only about a third of depressed patients as evidenced by elevated C-reactive protein (CRP) levels (Osimo et al., 2019). Patients with the same MDD diagnosis express very different symptom profiles that, in turn, may be associated to distinct pathophysiological mechanisms. Recently, we reviewed evidence (Milaneschi et al., 2020) suggesting that inflammatory and metabolic alterations map more consistently onto "atypical/energy-related" symptoms such as hypersomnia, hyperphagia, weight gain, fatigue and leaden paralysis. Converging findings from independent large-scale cohort studies (Milaneschi et al., 2020) showed that associations with several immune-metabolic markers (e.g. abdominal obesity, circulating levels of glucose, insulin, proinflammatory cytokines, and leptin) emerged only when contrasting control subjects with patients with an atypical/energy-related symptom profile, while they were weaker and statistically nonsignificant when considering all patients with an MDD diagnosis or other symptom profiles. It could be hypothesized that also TRYCATs levels may vary as a function of depression-related biological and clinical features, showing more consistent associations with circulating inflammatory markers and atypical/energy-related symptoms. We additionally considered two other clinical profiles based on melancholic symptoms, previously associated with lower TRP and higher KYN/TRP ratio in adolescents (Gabbay et al., 2010), and on the anxiety symptoms listed by the DSM-5 anxious-distress specifier, previously associated (Gaspersz et al., 2017) with higher inflammatory markers.

In the present study, leveraging unique data from a large, psychiatrically well-characterized cohort and taking important confounding factors into account, we examined the association of TRYCATs levels (TRP, KYN, KynA, QA and related ratios) with the presence of MDD and depression-related clinical (symptom profiles: atypical/energy-related, melancholic and anxious-distress) and biological (inflammatory markers: CRP, Interleukin-6 [IL-6] and TNF) features.

2. Methods

2.1. Study sample

Participants were from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing cohort study into the long-term course and consequences of depressive and anxiety disorders. A description of the study rationale, design, and methods is given elsewhere (Penninx et al., 2008). Briefly, in 2004 to 2007, 2981 participants with depressive and/or anxiety disorder and healthy control subjects were recruited from the community (19%), general practice (54%), and secondary mental health care (27%), therefore reflecting various settings and developmental stages of psychopathology. Exclusion criteria were: 1) a clinically overt primary diagnosis of other psychiatric disorders not subject of NESDA which could substantially affect course trajectory: psychotic disorders, obsessive–compulsive disorder, bipolar disorder or addiction disorder; 2) not being fluent in Dutch. The research protocol was approved by the ethical committee of participating universities, and all respondents provided written informed consent.

The presence of DSM-IV diagnosis of MDD was assessed using the Composite Interview Diagnostic Instrument version 2.1 (Wittchen, 1994) administered by specially trained research staff. The analytical sample included 2495 subjects with measures of circulating TRYCATs and categorized as follow: 1100 participants with current (that is, within the past 6 month) and 753 with remitted (lifetime but not current) MDD, and 642 healthy controls (without any lifetime depressive/anxiety disorder).

2.2. Blood measures

Circulating inflammatory markers and TRYCATs were determined from fasting morning blood plasma. For all markers, assessment platforms and technical parameters are described in details in previous publications (Vogelzangs et al., 2012; Lamers et al., 2019) and supplemental methods. Inflammatory markers included CRP, IL-6 and TNF. TRYCATs included TRP, KYN, KynA and QA. Among the assessed TRYCATs, TRP and KYN were previously measured in NESDA on a different platform for specific analyses (Quak et al., 2014; Sorgdrager et al., 2017). A comparison between previous and current measures is described in supplemental methods. Different ratios were calculated indexing overall KP activation (KYN/TRP), or its switch towards more neurotoxic (QA/KYN) or neuroprotective (KynA/KYN) TRYCATs and their relative balance (QA/KynA).

2.3. Depression symptom profiles

Three depression symptom profiles were created as described in a previous study (Lamers et al., 2020). The atypical, energy-related symptom (AES) and melancholic symptom (MS) profiles were based on sum scores of items extracted from the self-report Inventory of Depressive Symptomatology (IDS-SR_{30}) (Rush et al., 1996). The AES score (0-15range), was based on items we consider as belonging to the Immuno-Metabolic Depression (IMD) domain (Milaneschi et al., 2020): increased appetite, increased weight, hypersomnia, leaden paralysis and low energy. The MS score (0-24range) included melancholic features (Khan et al., 2006): diurnal variation (mood worse in the morning), early morning awakening, distinct quality of mood, excessive guilt, decreased appetite, decreased weight, psychomotor agitation and psychomotor retardation. An anxious distress symptom (ADS, 0–15 range) score was constructed using items from the IDS-SR_{30} (feeling tense, restlessness, concentration/worrying) and the Beck Anxiety Inventory (fear of awful events, feeling like losing control) (Beck et al., 1988) matching with the five criteria for the DSM-5 anxious distress specifier (Gaspersz et al., 2017).

2.4. Covariates

Sociodemographic characteristics included age, sex, and years of education. The following lifestyle characteristics were assessed: being a current smoker; alcohol consumption measured as drinks/week and categorized as nondrinker, mild-moderate drinker, (1–14 women/1–21 men), and heavy drinker (>14 women / >21 men). Number of self-reported chronic diseases (0/1/2+) for which persons received treatment (including cardiovascular disorders, diabetes, lung disease, osteoarthritis, cancer, ulcer, intestinal or liver diseases, epilepsy, and thyroid gland disease) was calculated as a global marker of poor physical health. BMI was calculated from weight and height measures. The use of medication was based on container inspection of drugs used in the past month and classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Selected medications were considered when taken on a regular basis (at least 50% of the time) and included antidepressants (ADs), classified in three sub categories: 1) selective serotonin reuptake inhibitors (SSRI, N06AB), 2) tricyclic antidepressants (TCA, N06AA) and 3) other antidepressants, including other less commonly prescribed drugs such as serotonin-norepinephrine reuptake inhibitors (N06AX), monoamine oxidase inhibitor nonselective (N06AF) or monoamine oxidase A inhibitor (N06AG). ADs were used by around

one quarter of the participants (18.1% SSRI, 2.8% TCA and 6.0% others). Furthermore, we considered non-steroidal anti-inflammatory medication (NSAIDs) used by 4.1% of the participants, including anti-inflammatory and anti-rheumatic preparations (M01A) used also in combination with corticosteroids (M01B), anti-allergic agents (A07EB), and aminosalicylic acid and similar agents (A07EC).

2.5. Statistical analyses

In descriptive analyses differences in characteristics across MDD status groups were tested using chi-square tests or analyses of variance. Concentrations of inflammatory markers were log-transformed for analyses due to skewed distribution. Pairwise correlations between TRYCATs and between inflammatory markers and symptom profiles were expressed as Pearson's coefficient.

Three sets of main analyses were performed. In the first, differences in mean TRYCATs levels across groups (controls, remitted MDD and current MDD) were tested using analyses of (co-)variance. Pairwise post-hoc comparisons were performed and standardized mean differences between two groups were reported using Cohen's d. The second set of analyses estimated the association of TRYCATs with inflammatory markers and symptom profiles in the overall sample using linear regressions. In the third set of analyses, subjects with current MDD were stratified in two groups (low vs high endorsement) according to features associated with TRYCATs in the second step. Differences in mean TRYCATs levels across groups (controls, remitted MDD, current MDD with low- and current MDD with high feature endorsement) were tested using analyses of co-variance. Results from all analyses were presented as unadjusted (model 1) and adjusted for three sets of covariates: the first set (model 2) included potential sociodemographic, lifestyle and health-related confounders impacting on depression and inflammation/TRYCATs levels, namely age, sex, education, smoking status, alcohol consumption and chronic diseases. Two subsequent alternative models additionally included covariates sharing underlying mechanisms with depression and inflammation/TRYCATs, namely the use of NSAIDs or ADs medications (model 2A) or BMI (model 2B). These factors were tested separately considering their complex role and position occupied in the pathway linking depression and inflammation, which cannot be completely deconvoluted in observational data by simple statistical adjustment that, in turn, may represent an "over-adjustment" for relevant underlying mechanisms. Medication use may indeed tag merely depression severity for ADs or heightened pain and inflammation for NSAIDs, most likely representing the clinical indication for treatment (confounding by indication) (Kyriacou and Lewis, 2016). Furthermore, it is known that genetic variants for inflammatory markers (e.g. CRP, IL-6) and depression (e.g. NEGR1 [Neuronal Growth Regulator 1]) and alterations in biological pathways relevant for depression (including inflammation, the hypothalamic–pituitaryadrenal axis, neuroendocrine regulators of energy metabolism including leptin and insulin) have a major role in BMI pathophysiology. (Ligthart et al., 2018; Howard et al., 2019; Milaneschi et al., 2019).

Analyses were performed in R v4.0.0 (R Project for Statistical Computing). All statistical tests were two-sided and used a significance level of $P < 0.05$. False-Discovery Rate (FDR) q-values were calculated taking into account multiple testing using the 'p.adjust' function in R.

3. Results

3.1. Descriptives

The mean age of the study sample was 41.7 (±13.0) years, and 66.7% were females.

Subjects with an MDD diagnosis were more often women, older and less educated (Table 1). As compared to controls, currently depressed subjects had less favorable profiles on lifestyle and health characteristics, higher CRP levels and, as expected, higher severity in depressive symptom profiles. TRYCATs concentrations are illustrated in eFigure1 and eTable1. The pairwise correlations between all metabolites and related ratios are reported in Fig. 1.

Table 1
Main characteristics of the study sample according to diagnostic status.

Characteristics	Controls (N = 642)	MDD		P-overall
		Remitted (N = 753)	Current (N = 1100)	
Sociodemographics				
Age years (mean ± SD)	41.1 (14.7)	43.5 (12.5)	40.8 (12.1)	<0.001
Sex (F) (%)	61.7	70.0	67.5	0.004
Education years (mean ± SD)	12.8 (3.2)	12.4 (3.2)	11.6 (3.2)	
Lifestyles & Health				
Current smoker (%)	26.8	39.7	45.5	<0.001
Alcohol consumption (%)				<0.001
non-drinker	23.2	28.7	39.7	
mild-moderate	65.3	59.9	48.6	
heavy	11.5	11.4	11.6	
BMI (kg/m^2) (mean ± SD)	25.1 (4.6)	25.7 (4.9)	25.9 (5.5)	0.003
N of chronic diseases (%)				<0.001
0	64.6	58.0	53.7	
1	25.7	27.4	30.5	
2+	9.7	14.6	15.8	
Use of NSAIDs (%)	1.9	5.2	4.7	0.003
Clinical				
IDS-SR$_{30}$ (mean ± SD)	8.6 (7.5)	17.5 (10.0)	32.6 (12.2)	<0.001
AES (mean ± SD)	1.4 (1.7)	2.7 (2.2)	5.1 (2.7)	<0.001
MS (mean ± SD)	1.5 (2.0)	3.4 (3.1)	7.1 (3.6)	<0.001
ADS (mean ± SD)	1.2 (1.8)	3.2 (2.7)	6.1 (3.1)	<0.001
Use of ADs (%)	0.9	22.2	43.5	<0.001
Inflammatory markers				
CRP (mg/L) (mean ± SD)	2.4 (4.4)	2.7 (5.1)	3.1 (5.2)	0.002*
IL-6 (pg/ml) (mean ± SD)	1.3 (3.2)	1.3 (3.5)	1.3 (2.8)	0.13*
TNF (pg/ml) (mean ± SD)	1.1 (1.3)	1.0 (1.1)	1.2 (1.7)	0.27*

* P values from anova models based on log-transformed values.

3.2. Differences in TRYCATs across MDD groups

Across all TRYCATs and ratios a significant difference, although only at nominal α-level (all FDR-q > 0.05), between groups was found only for KynA (Table2, eFigure2) levels: these were significantly lower for current MDD cases as compared to controls (d = -0.14, $_{post\text{-}hoc}$-p = 0.004). This difference was substantially reduced (d = -0.04, $_{post\text{-}hoc}$-p = 0.48) in fully adjusted models (eTable2). Differences in TRYCATs and related ratios levels between controls and subjects with remitted MDD were all not statistically significant.

3.3. Associations of TRYCATs with symptom profiles and inflammatory markers

Correlations between inflammatory markers and symptom profiles are shown in eFigure3.

Supplemental eTables 3–6 shows unadjusted and adjusted estimates obtained through regressing TRYCATs levels on symptom profiles and inflammatory markers. Fig. 2 shows the statistically significant (FDR-q < 0.05; 48 tests) standardized estimates. The number of significant associations in unadjusted analyses (model 1) was 27, which was reduced to 22 after adjusting for age, sex, education, smoking status, alcohol consumption and chronic diseases (model 2). In the latter model, MS was associated with lower KynA (β = -0.05, se = 0.02, p = 1.1e-2), while AES was associated with higher TRP (β = 0.06, se = 0.02, p = 6.2e-3), KYN (β = 0.05, se = 0.02, p = 2.2e-2) and QA (β = 0.06, se = 0.02, p = 4.0e-3). Inflammatory markers were associated with higher KYN (CRP: β = 0.12, se = 0.02, p = 6.8e-10; IL-6: β = 0.08, se = 0.02, p = 5.7e-5; TNF: β = 0.10, se = 0.02, p = 1.3e-7), QA (CRP: β = 0.21, se = 0.02, p =

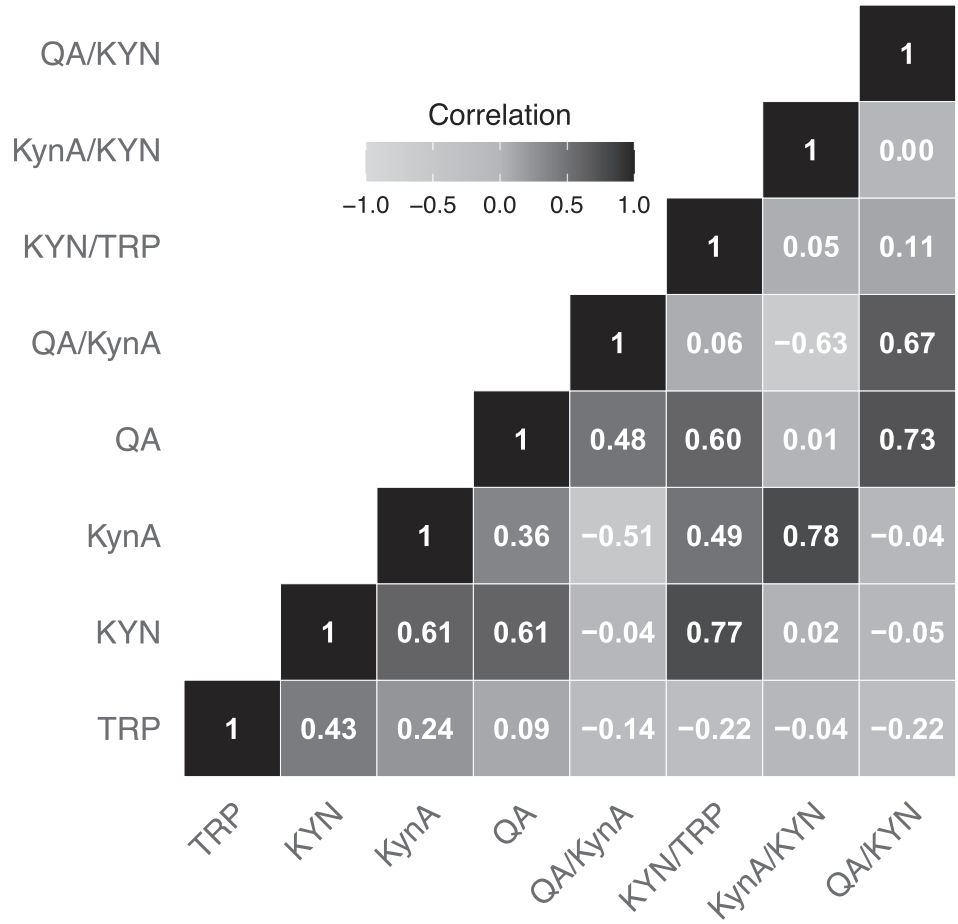

Fig. 1. Pairwise correlations between TRYCATs and related ratios.

Table 2
TRYCATs levels across diagnostic groups.

	Controls	MDD		
		Remitted	Current	
	(N = 642)	(N = 753)	(N = 1100)	P-overall
TRYCATs (mean ± SD)				
TRP (μmol/L)	60.5 (9.8)	60.1 (9.7)	60.7 (10.1)	0.41
KYN (μmol/L)	2.0 (0.5)	1.9 (0.5)	1.9 (0.5)	0.30
KynA (mmol/L)	45.8 (19.2)[a]	44.1 (18.3)	43.1 (19.1)[a]	0.02
QA (mmol/L)	385.4 (151.1)	375.5 (144.0)	376.0 (172.2)	0.42
TRYCATs – Ratios (mean ± SD)				
QA/KynA	9.4 (4.1)	9.5 (4.6)	9.7 (4.8)	0.35
KYN/TRP*	32.6 (7.5)	32.3 (7.1)	32.0 (8.3)	0.26
KynA/KYN	23.3 (7.3)	22.8 (7.4)	22.4 (7.6)	0.06
QA/KYN	198.3 (57.1)	195.9 (57.9)	196.0 (60.3)	0.68

All FDR-q > 0.05.
Model 1: adjusted for age, sex and education.
Model 2: additionally adjusted for smoking status, alcohol consumption, chronic diseases and use of NSAIDS.
*KYN/TRP estimates multiplied by 1000 to ease readability.
[a] Groups with significantly different means in post-hoc pairwise comparison.

1.9e-26; IL-6: β = 0.12, se = 0.02, p = 1.2e-9; TNF: β = 0.18, se = 0.02, p = 5.2e-21). Furthermore, all inflammatory markers were significantly associated with higher ratios indexing KP activity (KYN/TRP) or predominantly "neurotoxic" output (QA/KYN, QA/KynA), and with the lower ratio indexing predominantly "neuroprotective" output (KynA/KYN). Additional adjustment for ADs or NSAIDs use (model 2A) or BMI (model 2B) did not substantially impact the results profile (eFigure4), with the exception of the IL-6-KYN, AES-KYN and AES-QA associations, that were no longer statistically significant in BMI-adjusted models. While BMI-adjustment slightly weakened all estimates, those for TNF remained largely unchanged.

3.4. Stratifications of MDD cases

The variables associated to TRYCATs in the previous step were used to stratify the 1100 current MDD cases. Among these subjects, ~30% had CRP levels ≥ 3 mg/L, a commonly applied clinical cut-off (Osimo et al., 2019). Thus, values above the 7th deciles were used to stratify MDD cases across the other variables. Supplemental eTables 8–11 reports all criteria applied, exact numbers, and TRYCATs unadjusted (model 1) and adjusted (models 2,2A,2B) means in stratified MDD cases. Fig. 3 illustrates key significant results from model 2: as compared to healthy controls, significantly higher KYN and QA levels were found for MDD cases with high CRP (KYN: d = 0.20, $_{post\text{-}hoc}$p = 4.0e-3; QA: d = 0.33, $_{post\text{-}hoc}$p = 3.4e-6) and high TNF (KYN: d = 0.24, $_{post\text{-}hoc}$p = 8.2e-4; QA: d = 0.39, $_{post\text{-}hoc}$p = 8.3e-8). In contrast, MDD patients with lower inflammatory markers had lower KYN and QA levels as compared to both controls and MDD cases with high inflammation levels, highlighting the high degree of heterogeneity in TRYCATs within MDD. This results pattern extended to KYN/TRP, QA/KYN and QA/KynA ratios and showed similar directions (although statistically not significant) for the stratification according to AES (e.g. QA: high AES d = 0.09, low AES d = -0.08). The result pattern was similar after additional adjustment for medication use (model 2A, eTable 10) or BMI (model 2B, eTable 11).

4. Discussion

Using large-scale data from a well-established cohort, we examined

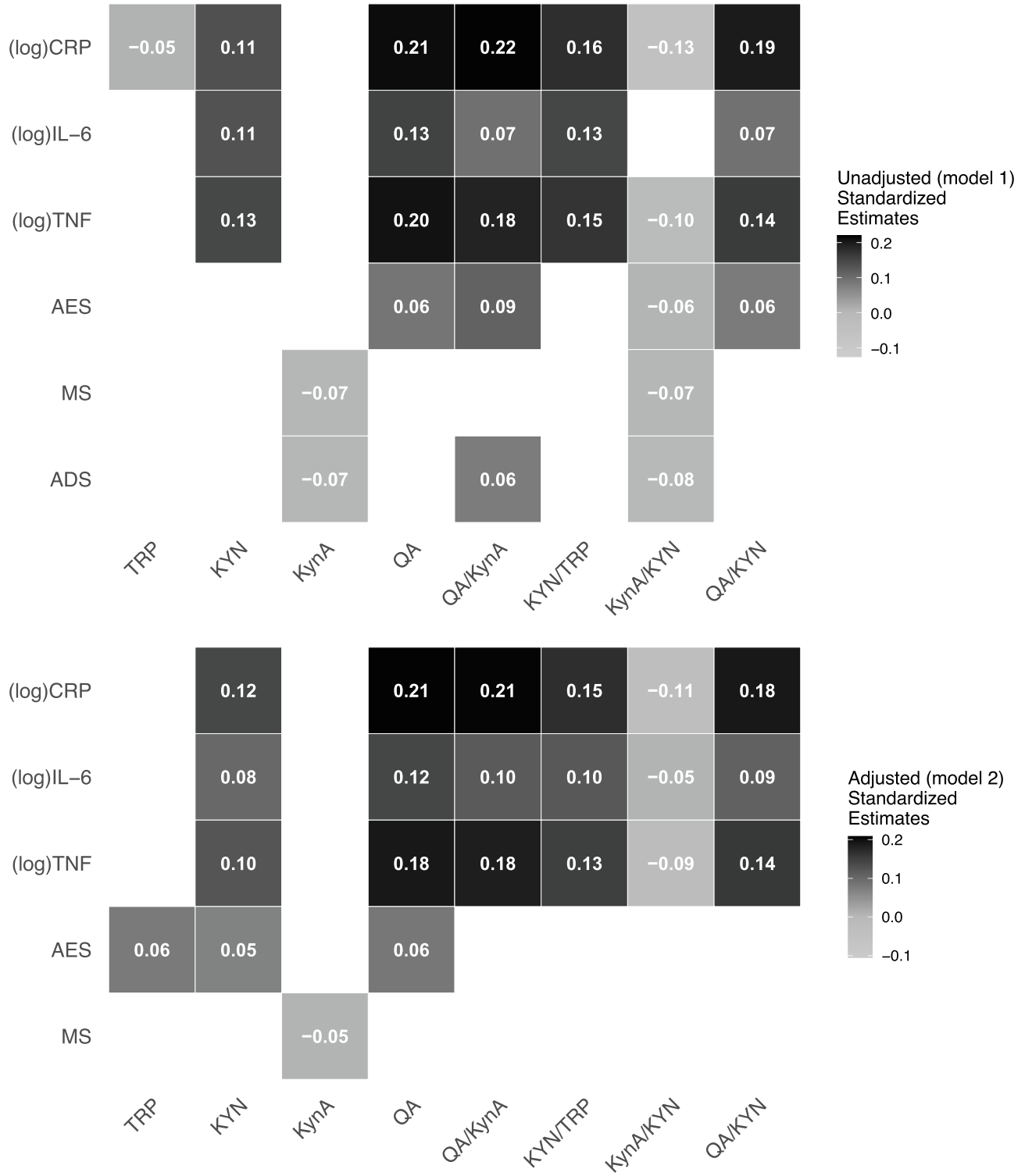

Fig. 2. Association of TRYCATs levels with inflammatory markers and symptom profiles. Full results available in supplemental eTable 3, 4. From linear regression models. Model 1: unadjusted. Model 2: adjusted for age, sex, education, smoking status, alcohol consumption and chronic diseases. Standardized estimates of statistically significant associations at FDR-q < 0.05 are reported.

the association of TRYCATs levels with MDD and depression-related clinical and biological features. Overall, TRYCATs levels were not associated with the presence of an MDD diagnosis, but varied as a function of circulating inflammatory markers and, to a lesser extent, of specific depressive symptom profiles.

Circulating TRYCATs in subjects with remitted and those with current MDD were not different from those of healthy controls. Levels of KynA were lower in MDD cases as compared to controls only in unadjusted analyses. Reduced KynA in depression has been reported by previous studies (Marx et al.), and it is consistent with its potential neuroprotective and anti-inflammatory actions (Savitz, 2020; Cervenka et al., 2017). Nevertheless, after taking into account key sociodemographic, lifestyle and health-related factors, a difference in KynA levels was no longer detectable. These results are not in line with those of a

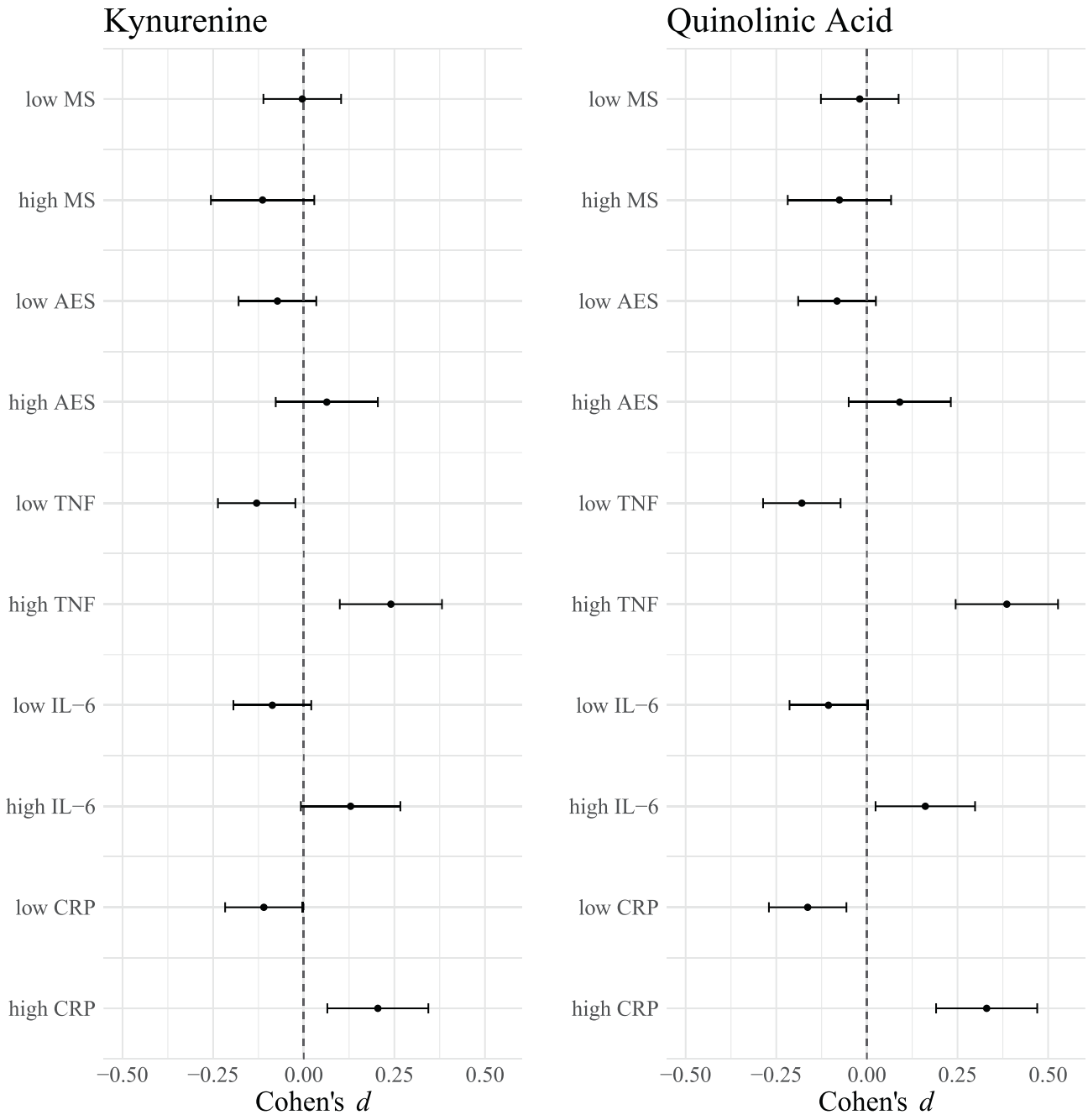

Fig. 3. Standardized mean differences in kynurenine and quinolinic acid versus healthy controls of current MDD cases stratified according to inflammatory markers and symptom profiles. Full results available in supplemental eTable 9. Adjusted means form analyses of co-variance adjusted for age, sex, education, smoking status, alcohol consumption and chronic diseases.

recent meta-analysis (Marx et al.), which reported lower levels of TRP, KYN, KynA, KynA/KYN in MDD cases as compared to controls. However, the overwhelming majority of studies included in the meta-analysis was of small size from highly selected clinical samples. In contrast, the present study was based on a large naturalistic cohort with MDD cases selected at different settings (community, general practice and secondary mental health care) and developmental stages of psychopathology, likely reflecting the wider variety of MDD patients in the population.

Higher circulating concentrations of inflammatory markers such as TNF and CRP were associated - independently from major confounders - with higher KYN, QA levels and ratios related to KP activation (KYN/TRP), especially toward "neurotoxic" output (QA/KYN, QA/KynA). These results are consistent with the triggering effect on KP of inflammatory signals (Bonaccorso et al., 2002; Capuron et al., 2003), in particular of TNF (O'Connor et al., 2009; Robinson et al., 2005). In a recent study (Haroon et al., 2020) on 72 unmedicated depressed patients, plasma TNF was robustly associated with KYN and KYN/TRP. The present findings showed a consistent associations between inflammatory markers and KP activation toward QA production, sustaining its potential role in linking inflammation to depression pathophysiology. In the central nervous system, QA binds to glutamate receptor and, in synergy with cytokine-induced glutamate release and reuptake reduction, increases excitotoxicity and decreases neurotrophic factors synthesis (Latif-Hernandez et al., 2016; Forrest et al., 2015; Savitz et al., 2015). Among symptom profiles, results of AES paralleled those of inflammatory markers in the relationship with KYN and QA, although with relatively smaller effect size. This is consistent with the IMD model we recently proposed (Milaneschi et al., 2020; Lamers et al., 2020),

characterized by the clustering of inflammatory/metabolic dysregulations and atypical symptoms characterized by altered energy intake/expenditure (hypersomnia, hyperphagia, weight gain, fatigue and leaden paralysis). Similarly, Haroon et al. (Haroon et al., 2020) showed that depressed patients with combined higher levels of TNF-KYN/TRP had higher scores in a scale including items coding for low energy and anhedonia, another depressive symptom previously postulated to be related to inflammation and neurotoxic TRP catabolites (Felger and Treadway, 2017; Savitz et al., 2015). In the present study, the AES profile was also associated with higher circulating TRP. The actual mechanism underlying this association is unknown; it could be only speculated that the increased energy intake expressed via the symptom of hyperphagia may determine a higher intake of food containing TRP, which could be acquired only from diet. A symptom profile characterized by melancholic symptoms, commonly found in severe forms of depression with suicidal and psychotic features, was instead specifically associated with decreased KynA levels. Interestingly, a previous study (Wurfel et al., 2017) showed significant reduction, as compared to healthy controls, of KynA levels in acutely ill inpatients with affective disorders, particularly in those with psychotic features. These results highlight the complexity of the kynurenine pathway, with key metabolites divergently associated with different depressive symptoms, reflecting specific biological signatures (Gold, 2015; Penninx et al., 2013). Previous evidence (Milaneschi et al., 2016) indicates substantial genetic overlap between psychiatric trait such as schizophrenia and melancholic-like forms of depression, linked in the present study to reduced KynA levels. In contrast, genetic signature of inflammatory and metabolic alterations characterize specifically atypical-like depressive symptoms (Milaneschi et al., 2017; Badini et al., 2020), linked in the present study to increased KYN and QUIN levels. Consistently, recent findings (Lamers et al., 2020) in NESDA based on the symptom profiles adopted in the present study, confirmed that several inflammatory (i.e. CRP and IL-6) and metabolic (i.e. fasting glucose, HDL cholesterol, triglycerides, blood pressure and waist circumference) markers were specifically associated with the atypical/energy-related symptom profile, but not with the melancholic profile. Finally, no association was found for the ADS profile, suggesting reduced relevance for TRYCATs in anxiety. This observation is in line with results of a large-scale study (Milaneschi et al., 2021) involving NESDA and UK Biobank, which showed strong associations of inflammatory markers with specific depressive symptoms (low mood, anhedonia, fatigue, altered sleep and appetite changes), but less consistent associations with anxiety symptoms.

Overall, the association of TRYCATs with depression symptom profiles and inflammatory markers was partially explained by sociodemographic, lifestyle and health-related factors, as indicated by the reduction of estimates in adjusted models. Including the use of ADs and NSAIDs medications in statistical models had no appreciable impact on all the associations detected. This is consistent with a previous meta-analyses (Arnone et al., 2018), in which the results of lower KYN levels in MDD vs controls was not explained by the number of AD-medicated individuals across studies. Nevertheless, it is difficult to clearly disentangle the effect of medications from that of depression or inflammation severity in observational studies; future clinical trials measuring TRYCATs are needed to dissect the specific effect of medications. Additional adjustment for BMI reduced the strength of the associations for CRP, IL-6 and the AES profile. This impact is consistent with the complex shared pathways and substantial genetic covariance shown (Milaneschi et al., 2017, 2021; Badini et al., 2020; Kappelmann et al., 2021) to connect BMI, inflammatory markers such as CRP and IL-6 and atypical symptoms. Associations estimates for TNF were instead substantially unchanged after adjustment for BMI, suggesting a partially distinct inflammatory pathway connected with TRP metabolism.

Finally, findings from the present study highlighted the heterogeneity in circulating TRYCATs within MDD patients. Significantly higher markers of KP activation toward neurotoxic metabolites (KYN, QA, KYN/TRP, QA/KYN, QA/KynA) in MDD patients as compared to controls emerged only when selecting cases with high blood pro-inflammatory markers. In contrast, patients with lower pro-inflammatory markers had even lower TRYCATs as compared to controls. Similarly to most studied biomarkers of depression (Milaneschi et al., 2020), dysregulation of the KP may be limited to specific subgroups of patients. This picture is consistent with evidence from previous meta-analyses (Milaneschi et al., 2020; Penninx et al., 2013) examining biomarkers of inflammation, metabolic syndrome and hypothalamic–pituitaryadrenal axis, showing small averages difference between MDD cases and controls, but large individual differences. Consistently, in the present study effect sizes obtained from selecting MDD cases were of small-to-medium entity (e.g. MDD with high TNF d = 0.4).

Strengths of the present study included the large sample with detailed psychiatric assessment and the availability of a wider array of important confounders. A major limitation was the cross-sectional design, precluding any causal inferences to be derived from the results. Furthermore, we only measured peripheral TRYCATs levels. Nevertheless, previous studies in different neuropsychiatric conditions (Haroon et al., 2020; Jacobs et al., 2019; Sellgren et al., 2019) showed that TRYCATs levels in blood and in the cerebrospinal fluid are strongly correlated. This is consistent with the biological model postulating that the larger proportion of KYN in the brain is actively transported from the periphery, and later centrally converted in QA by microglia and infiltrated macrophages (Savitz, 2020). Finally, the lack of dietary assessments, in particular with regard to TRP nutritional intake and the use of amino-acid supplements, did not allow us to examine the impact of eating behaviors on TRP levels.

While it is currently impossible to determine whether any changes in blood TRYCATs are due to peripheral processes only or may be influenced by low-grade inflammation in the brain, dysregulation of KP is a biologically plausible candidate in depression pathophysiology. Furthermore, the documented impact of TRYCATs on various immunological, metabolic and endocrine processes (Cervenka et al., 2017) may represent a relevant link with somatic conditions commonly comorbid with depression. Thus, TRYCATs are advocated as a promising target for pharmacological (e.g. IDO inhibitors (Liu et al., 2018) or behavioral (e.g. exercise (Agudelo et al., 2014) interventions. As the results of the study suggest, KP modulation could be of potential benefit for a specific subset of depressed subjects. Future clinical studies should focus on subgroup of patients with clear evidence of dysregulation in the kynurenine pathway.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Dr. Milaneschi reported no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.07.007.

References

Savitz, J., 2020. The kynurenine pathway: a finger in every pie. Mol. Psychiatry 25 (1), 131–147.

Cervenka, I., Agudelo, L.Z., Ruas, J.L., Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health. Science (80-). 2017;357(6349).

Haroon, E., Raison, C.L., Miller, A.H., Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. Neuropsychopharmacology [Internet]. 2012;37(1): 137–62. Available from: doi: 10.1038/npp.2011.205.

Dantzer, R., 2017. Role of the kynurenine metabolism pathway in inflammation-induced depression: preclinical approaches. Curr. Top. Behav. Neurosci. 31, 117–138.

O'Connor, J.C., André, C., Wang, Y., Lawson, M.A., Szegedi, S.S., Lestage, J., et al., 2009. Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. J. Neurosci. 29 (13), 4200–4209.

Robinson, C.M., Hale, P.T., Carlin, J.M., 2005. The role of IFN-gamma and TNF-alpha-responsive regulatory elements in the synergistic induction of indoleamine dioxygenase. J. Interf. Cytokine Res. Off. J. Int. Soc. Interf. Cytokine Res. 25 (1), 20–30.

Latif-Hernandez, A., Shah, D., Ahmed, T., Lo, A.C., Callaerts-Vegh, Z., Van der Linden, A., Balschun, D., D'Hooge, R., 2016. Quinolinic acid injection in mouse medial prefrontal cortex affects reversal learning abilities, cortical connectivity and hippocampal synaptic plasticity. Sci. Rep. 6 (1) https://doi.org/10.1038/srep36489.

Forrest, C.M., McNair, K., Pisar, M., Khalil, O.S., Darlington, L.G., Stone, T.W., 2015. Altered hippocampal plasticity by prenatal kynurenine administration, kynurenine-3-monoxygenase (KMO) deletion or galantamine. Neuroscience 310, 91–105.

Savitz, J., Drevets, W.C., Smith, C.M., Victor, T.A., Wurfel, B.E., Bellgowan, P.SF., Bodurka, J., Teague, T.K., Dantzer, R., 2015. Putative neuroprotective and neurotoxic kynurenine pathway metabolites are associated with hippocampal and amygdalar volumes in subjects with major depressive disorder. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 40 (2), 463–471.

Marx W, Mcguinness AJ, Rocks T, Ruusunen A, Cleminson J, Walker AJ, et al. The kynurenine pathway in major depressive disorder , bipolar disorder , and schizophrenia : a meta-analysis of 101 studies. Mol Psychiatry [Internet]. Available from: https://doi.org/10.1038/s41380-020-00951-9.

Osimo, E.F., Baxter, L.J., Lewis, G., Jones, P.B., Khandaker, G.M., 2019. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol. Med. 49 (12), 1958–1970.

Milaneschi, Y., Lamers, F., Berk, M., Penninx, B.W.J.H., 2020. Depression heterogeneity and its biological underpinnings: toward immunometabolic depression. Biol. Psychiatry 88 (5), 369–380.

Gabbay, V., Klein, R.G., Katz, Y., Mendoza, S., Guttman, L.E., Alonso, C.M., et al., The possible role of the kynurenine pathway in adolescent depression with melancholic features. J. Child. Psychol. Psychiatry Allied Discip. 2010;51(8):935–43.

Gaspersz, R., Lamers, F., Wittenberg, G., Beekman, A.T.F., van Hemert, A.M., Schoevers, R.A., Penninx, B.W.J.H., 2017. The role of anxious distress in immune dysregulation in patients with major depressive disorder. Transl. Psychiatry 7 (12). https://doi.org/10.1038/s41398-017-0016-3.

Penninx, B.W.J.H., Beekman, A.T.F., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., De Jong, P.J., Van Marwijk, H.W.J., Assendelft, W.J.J., Van Der Meer, K., Verhaak, P., Wensing, M., De Graaf, R., Hoogendijk, W.J., Ormel, J., Van Dyck, R., 2008. The Netherlands Study of Depression and Anxiety (NESDA): Rationale, objectives and methods. Int. J. Methods Psychiatr. Res. 17 (3), 121–140.

Wittchen, H.-U., 1994. Reliability and validity studies of the WHO–Composite International Diagnostic Interview (CIDI): a critical review. J. Psychiatr. Res. 28 (1), 57–84.

Vogelzangs, N., Duivis, H.E., Beekman, A.T.F., Kluft, C., Neuteboom, J., Hoogendijk, W., et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl Psychiatry [Internet]. 2012;2 (2):e79-9. Available from: doi: 10.1038/tp.2012.8.

Lamers, F., Milaneschi, Y., Smit, J.H., Schoevers, R.A., Wittenberg, G., Penninx, B.W.J.H., Longitudinal Association Between Depression and Inflammatory Markers: Results From the Netherlands Study of Depression and Anxiety. Biol Psychiatry [Internet]. 2019;85(10):829–37. Available from: https://doi.org/10.1016/j.biopsych.2018.12.020.

Quak, J., Doornbos, B., Roest, A.M., Duivis, H.E., Vogelzangs, N., Nolen, W.A., Penninx, B.W.J.H., Kema, I.P., de Jonge, P., 2014. Does tryptophan degradation along the kynurenine pathway mediate the association between pro-inflammatory immune activity and depressive symptoms? Psychoneuroendocrinology 45, 202–210.

Sorgdrager, F.J.H., Doornbos, B., Penninx, B.W.J.H., de Jonge, P., Kema, I.P., 2017. The association between the hypothalamic pituitary adrenal axis and tryptophan metabolism in persons with recurrent major depressive disorder and healthy controls. J. Affect. Disord. 222 (June), 32–39.

Lamers, F., Milaneschi, Y., Vinkers, C.H., Schoevers, R.A., Giltay, E.J., Penninx, B.W.J.H., 2020. Depression profilers and immuno-metabolic dysregulation: Longitudinal results from the NESDA study. Brain Behav. Immun. 88, 174–183.

Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol. Med. 26 (3), 477–486.

Khan, A.Y., Carrithers, J., Preskorn, S.H., Lear, R., Wisniewski, S.R., John Rush, A., et al. Clinical and demographic factors associated with DSM-IV melancholic depression. Ann. Clin. Psychiatry Off. J. Am. Acad. Clin. Psychiatr. 2006;18(2):91–8.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988 Dec. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56 (6), 893–897.

Kyriacou, D.N., Lewis, R.J., 2016. Confounding by indication in clinical research. JAMA – J. Am. Med. Assoc. 316 (17), 1818. https://doi.org/10.1001/jama.2016.16435.

Ligthart, S., Vaez, A., Võsa, U., Stathopoulou, M.G., de Vries, P.S., Prins, B.P., et al., 2018. Genome analyses of >200,000 individuals identify 58 loci for chronic inflammation and highlight pathways that link inflammation and complex disorders. Available from Am. J. Hum. Genet. [Internet] 103 (5), 691–706. https://linkinghub.elsevier.com/retrieve/pii/S0002929718303203.

Howard, D.M., Adams, M.J., Clarke, T.K., Hafferty, J.D., Gibson, J., Shirali, M., et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci [Internet]. 2019;22(3):343–52. Available from: https://doi.org/10.1038/s41593-018-0326-7.

Milaneschi, Y., Simmons, W.K., van Rossum, E.F.C., Penninx, B.WJH., 2019. Depression and obesity: evidence of shared biological mechanisms. Mol. Psychiatry 24 (1), 18–33.

Bonaccorso, S., Marino, V., Puzella, A., Pasquini, M., Biondi, M., Artini, M., et al., 2002. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. J. Clin. Psychopharmacol. 22 (1), 86–90.

Capuron, L., Neurauter, G., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Fuchs, D., Miller, A.H., 2003. Interferon-alpha-induced changes in tryptophan metabolism. Relationship to depression and paroxetine treatment. Biol. Psychiatry 54 (9), 906–914.

Haroon, E., Welle, J.R., Woolwine, B.J., Goldsmith, D.R., Baer, W., Patel, T., Felger, J.C., Miller, A.H., 2020. Associations among peripheral and central kynurenine pathway metabolites and inflammation in depression. Neuropsychopharmacology 45 (6), 998–1007.

Felger, J.C., Treadway, M.T., Inflammation Effects on Motivation and Motor Activity: Role of Dopamine. Neuropsychopharmacology [Internet]. 2017;42(1):216–41. Available from: https://doi.org/10.1038/npp.2016.143.

Savitz, J., Dantzer, R., Meier, T.B., Wurfel, B.E., Victor, T.A., McIntosh, S.A., Ford, B.N., Morris, H.M., Bodurka, J., Teague, T.K., Drevets, W.C., 2015. Activation of the kynurenine pathway is associated with striatal volume in major depressive disorder. Psychoneuroendocrinology. 62, 54–58.

Wurfel, B.E., Drevets, W.C., Bliss, S.A., McMillin, J.R., Suzuki, H., Ford, B.N., et al., Serum kynurenic acid is reduced in affective psychosis. Transl. Psychiatry 2017;7(5).

Gold, P.W., The organization of the stress system and its dysregulation in depressive illness. Mol Psychiatry [Internet]. 2015 Feb 9 [cited 2017 Sep 5];20(1):32–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25486982.

Penninx, B.W.J.H., Milaneschi, Y., Lamers, F., Vogelzangs, N., Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med [Internet]. 2013 May 15 [cited 2017 Apr 20];11:129. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23672628.

Milaneschi, Y., Lamers, F., Peyrot, W.J., Abdellaoui, A., Willemsen, G., Hottenga, J.-J., Jansen, R., Mbarek, H., Dehghan, A., Lu, C., Boomsma, D.I., Penninx, B.W.J.H., 2016. Polygenic dissection of major depression clinical heterogeneity. Mol. Psychiatry [Internet] 21 (4), 516–522.

Milaneschi, Y., Lamers, F., Peyrot, W.J., Baune, B.T., Breen, G., Dehghan, A., Forstner, A. J., Grabe, H.J., Homuth, G., Kan, C., Lewis, C., Mullins, N., Nauck, M., Pistis, G., Preisig, M., Rivera, M., Rietschel, M., Streit, F., Strohmaier, J., Teumer, A., Van der Auwera, S., Wray, N.R., Boomsma, D.I., Penninx, B.W.J.H., 2017. Genetic association of major depression with atypical features and obesity-related

immunometabolic dysregulations. JAMA Psychiatry 74 (12), 1214. https://doi.org/10.1001/jamapsychiatry.2017.3016.

Badini, I., Coleman, J.R., Hagenaars, S.P., Hotopf, M., Breen, G., Lewis, C.M., et al., 2020. Depression with atypical neurovegetative symptoms shares genetic predisposition with immuno-metabolic traits and alcohol consumption. Psychol. Med. 1–11.

Milaneschi, Y., Kappelmann, N., Ye, Z., Lamers, F., Moser, S., Jones, P.B., et al., Association of Inflammation with Depression and Anxiety: Evidence for Symptom-Specificity and Potential Causality from UK Biobank and NESDA Cohorts. Mol Psychiatry. 2021 Jun 16. doi: 10.1038/s41380-021-01188-w. Epub ahead of print. PMID: 34135474.

Arnone, D., Saraykar, S., Salem, H., Teixeira, A.L., Dantzer, R., Selvaraj, S., 2018. Role of Kynurenine pathway and its metabolites in mood disorders: A systematic review and meta-analysis of clinical studies. Neurosci. Biobehav. Rev. 92, 477–485.

Badini, I., Coleman, J.R., Hagenaars, S.P., Hotopf, M., Breen, G., Lewis, C.M., et al. Depression with atypical neurovegetative symptoms shares genetic predisposition with immuno-metabolic traits and alcohol consumption. medRxiv. 2020; 2020.02.18.20024091.

Kappelmann, N., Arloth, J., Georgakis, M.K., Czamara, D., Rost, N., Ligthart, S., Khandaker, G.M., Binder, E.B., 2021. Dissecting the association between inflammation, metabolic dysregulation, and specific depressive symptoms: a genetic correlation and 2-sample mendelian randomization study. JAMA Psychiatry 78 (2), 161. https://doi.org/10.1001/jamapsychiatry.2020.3436.

Milaneschi, Y., Lamers, F., Penninx, B.W.J.H., 2021. Dissecting depression biological and clinical heterogeneity-the importance of symptom assessment resolution. JAMA Psychiatry 78 (3), 341. https://doi.org/10.1001/jamapsychiatry.2020.4373.

Jacobs, K.R., Lim, C.K., Blennow, K., Zetterberg, H., Chatterjee, P., Martins, R.N., Brew, B.J., Guillemin, G.J., Lovejoy, D.B., 2019. Correlation between plasma and CSF concentrations of kynurenine pathway metabolites in Alzheimer's disease and relationship to amyloid-β and tau. Neurobiol. Aging 80, 11–20.

Sellgren, C.M., Gracias, J., Jungholm, O., Perlis, R.H., Engberg, G., Schwieler, L., Landen, M., Erhardt, S., 2019. Peripheral and central levels of kynurenic acid in bipolar disorder subjects and healthy controls. Transl. Psychiatry 9 (1). https://doi.org/10.1038/s41398-019-0378-9.

Liu, M., Wang, X.u., Wang, L., Ma, X., Gong, Z., Zhang, S., Li, Y., 2018. Targeting the IDO1 pathway in cancer: from bench to bedside. J Hematol Oncol. 11 (1) https://doi.org/10.1186/s13045-018-0644-y.

Agudelo, L., Femenía, T., Orhan, F., Porsmyr-Palmertz, M., Goiny, M., Martinez-Redondo, V., Correia, J., Izadi, M., Bhat, M., Schuppe-Koistinen, I., Pettersson, A., Ferreira, D.S., Krook, A., Barres, R., Zierath, J., Erhardt, S., Lindskog, M., Ruas, J., 2014. Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. Cell 159 (1), 33–45.