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ARTICLE

The kynurenine pathway in major depressive disorder, bipolar disorder, and schizophrenia: a meta-analysis of 101 studies

Wolfgang Marx[1] · Amelia J. McGuinness[1] · Tetyana Rocks[1] · Anu Ruusunen[1,2,3] · Jasmine Cleminson[1] · Adam J. Walker[1] · Susana Gomes-da-Costa[4] · Melissa Lane[1] · Marsal Sanches[5,6] · Alexandre P. Diaz[5,6] · Ping-Tao Tseng[7] · Pao-Yen Lin[8,9] · Michael Berk[1] · Gerard Clarke[10] · Adrienne O'Neil[1] · Felice Jacka[1] · Brendon Stubbs[11,12] · André F. Carvalho[13,14] · João Quevedo[5,6] · Jair C. Soares[5,6] · Brisa S. Fernandes[5,6]

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Abstract

The importance of tryptophan as a precursor for neuroactive compounds has long been acknowledged. The metabolism of tryptophan along the kynurenine pathway and its involvement in mental disorders is an emerging area in psychiatry. We performed a meta-analysis to examine the differences in kynurenine metabolites in major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ). Electronic databases were searched for studies that assessed metabolites involved in the kynurenine pathway (tryptophan, kynurenine, kynurenic acid, quinolinic acid, 3-hydroxykynurenine, and their associate ratios) in people with MDD, SZ, or BD, compared to controls. We computed the difference in metabolite concentrations between people with MDD, BD, or SZ, and controls, presented as Hedges' g with 95% confidence intervals. A total of 101 studies with 10,912 participants were included. Tryptophan and kynurenine are decreased across MDD, BD, and SZ; kynurenic acid and the kynurenic acid to quinolinic acid ratio are decreased in mood disorders (i.e., MDD and BD), whereas kynurenic acid is not altered in SZ; kynurenic acid to 3-hydroxykynurenine ratio is decreased in MDD but not SZ. Kynurenic acid to kynurenine ratio is decreased in MDD and SZ, and the kynurenine to tryptophan ratio is increased in MDD and SZ. Our results suggest that there is a shift in the tryptophan metabolism from serotonin to the kynurenine pathway, across these psychiatric disorders. In addition, a differential pattern exists between mood disorders and SZ, with a preferential metabolism of kynurenine to the potentially neurotoxic quinolinic acid instead of the neuroprotective kynurenic acid in mood disorders but not in SZ.

Introduction

The importance of tryptophan as a precursor for neuroactive compounds has long been acknowledged. The metabolism of tryptophan along the kynurenine pathway and its possible involvement in the pathophysiology of mental disorders is an emerging area in psychiatry [1–5]. Alongside the biosynthesis of serotonin, an estimated 90% of tryptophan is metabolized via the kynurenine pathway [6]. Humans lack the ability to synthesize tryptophan, which has to be acquired from diet [7]. Tryptophan is initially metabolized to kynurenine via the rate-limiting enzymes tryptophan 2,3-dioxygenase (TDO, stress responsive) and indoleamine 2,3-dioxygenase (IDO1, immune responsive). Within the central nervous system (CNS), kynurenine is converted to 3-hydroxyanthranilic acid via anthranilic acid or 3-hydroxykynurenine, and subsequently into quinolinic acid in the microglia. This pathway has been linked with neurotoxicity,

These authors contributed equally: Wolfgang Marx, Amelia J. McGuinness

These authors jointly supervised this work: Brisa S. Fernandes, Jair C. Soares

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✉ Wolfgang Marx
wolf.marx@deakin.edu.au

✉ Brisa S. Fernandes
brisasf@gmail.com

Extended author information available on the last page of the article

via free radical generation contributing to oxidative stress, and the excitotoxic effects of quinolinic acid as a glutamate N-methyl-D-aspartate (NMDA) receptor agonist [8, 9]. Conversely, in astrocytes, kynurenine is converted to kynurenic acid, which has neuroprotective potential, both via NMDA and α7 nicotinic acetylcholine receptors antagonism, as well as through its anti-inflammatory and immunosuppressive functions [7, 9, 10].

Existing preclinical and clinical data suggest that dysregulation of the metabolic fate of tryptophan via the kynurenine pathway may be implicated in a range of severe psychiatric disorders, including: major depressive disorder (MDD) [2], bipolar disorder (BD), and schizophrenia (SZ) [11]. The kynurenine pathway is also influenced by inflammation [12] wherein a pro-inflammatory state can divert tryptophan metabolism towards the kynurenine pathway and away from serotonin production [1]. It is hypothesized that mental disorders are associated with the preferential switch in kynurenine metabolism to favour production of the neurotoxic quinolinic acid metabolite in detriment of the conceptually neuroprotective kynurenic acid in mood disorders and with a switch in favor of kynurenic acid in SZ [1].

Inflammation-associated influx of pro-inflammatory molecules into the brain can amplify macrophage infiltration; these cells have an ~30-fold increased capacity to produce quinolinic acid compared to microglia [13, 14]. The accumulation of quinolinic acid may over-stimulate glutamate receptors resulting in neuronal damage [15], and has been implicated in the often persistent nature of MDD. Conversely, an *increase* in kynurenic acid has been implicated in BD and SZ, despite theoretical neuroprotection [16]. Some studies have shown that concentrations of kynurenic acid in the cerebrospinal fluid (CSF) are increased in BD and SZ [17–19]. Induction and exacerbation of schizophrenia-like symptoms by other NMDA receptor antagonists such as ketamine support the hypothesis of the influence of kynurenic acid on positive symptoms of SZ [20, 21]. Although human studies reporting associations between kynurenic acid levels and SZ behaviour are inconsistent, manipulation of kynurenic acid levels in animal studies support involvement of kynurenic acid, with increased concentrations causing significant cognitive impairment, and reductions potentially resulting in cognitive improvement [22].

Due to the growing number of human studies that have compared the level of kynurenine pathway metabolites in people with mental disorders to healthy controls, some meta-analyses have previously been conducted [22–24]. However, those reviews included a relatively small number of studies, focused on a narrow range of metabolites, and/or examined only one psychiatric disorder. In this systematic review and meta-analysis, we aim to build upon previous work by examining blood levels of an extended range of kynurenine metabolites and metabolite ratios (e.g., kynurenine to tryptophan ratio) across three major mental disorders: MDD, BD, and SZ. Furthermore, we sought to explore the influence of blood source and demographic factors that influence kynurenine metabolism via sub-group and meta-regression analyses.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. Electronic databases (Embase, PubMed, and the Cochrane database) were systematically searched from journal inception until June 2019 to identify peer-reviewed studies that assessed kynurenine metabolites (i.e., tryptophan, kynurenine, kynurenic acid, quinolinic acid, 3-hydroxykynurenine, and their associate ratios) in people with either MDD, SZ, or BD, compared to healthy controls. The search terms related to kynurenine metabolites (e.g., kynurenine, tryptophan, indoleamine 2,3-dioxygenase) and mental disorders (e.g., depression, psychosis, schizophrenia). See Supplementary Material for full search terms used. The reference list of major reviews and prior meta-analyses on the topic were also searched for eligible studies.

Study selection

Eligible studies were those: (1) published in English; (2) observational studies including participants with MDD, BD (in any mood state) or SZ, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) criteria, compared to healthy controls; (3) measuring tryptophan or any metabolite of the kynurenine pathway in blood (plasma or serum) including kynurenine, kynurenic acid, quinolinic acid, 3-hydroxykynurenine, as well as the ratio of these metabolites (i.e., kynurenine/tryptophan ratio, kynurenic acid/quinolinic acid ratio, and kynurenic acid/kynurenine, and kynurenic acid/3-hydroxykynurenine). Studies that reported mixed data (e.g., a combined sample with >1 of the following populations: MDD, BD, and/or SZ) where outcomes were not disaggregated by diagnosis were excluded; however, studies that combined people with SZ and schizoaffective disorders were included. Studies were also excluded if they measured genetic outcomes only, included samples with other chronic diseases (e.g., celiac disease) or substance abuse diagnoses; or did not include a healthy control comparison group; reviews, abstracts, conference papers, and study protocols were also excluded. If two or more manuscripts reported on the same or

overlapping participant samples, data were only extracted for the manuscript that included the largest sample size.

Four investigators independently conducted the searches using Covidence Systematic Review Software. Authors first screened for eligibility based on titles and abstracts according to the eligibility criteria. Articles for which this was unclear were carried forward into the full-text review. The full-text of the remaining papers was independently reviewed by two authors, and eligible studies were included. Disagreements were managed by discussion to reach consensus.

Data extraction

The following data were extracted: study design, key characteristics of participants (e.g., age and sex), outcomes of interest, and key results (means, standard deviations, sample size, and/or p values) of the metabolites. Where results were reported as median and interquartile range, these were converted to mean and standard deviation using the formula proposed by Wan et al. [26] and Lou et al. [27].

Statistical Analyses

The meta-analyses were conducted in Comprehensive Meta-Analysis 3.0 [28] using a random-effects model [29] to account for possible heterogeneity between studies. The following outcomes were explored in separate meta-analyses: (1) The difference in metabolite concentrations between people with MDD, BD, or SZ, and healthy controls, presented as Hedges' g (with 95% confidence intervals (CI)). For studies that compared different clinical groups to the same group of healthy controls, an averaged effect size (ES) across all clinical groups was computed and used in the pooled analysis. (2) Potential moderators: When there were a sufficient number of studies, effect modifiers including clinical population, age, sex distribution, and blood sample type (plasma or serum) were examined using sub-group analyses and meta-regressions (when at least 3 and 10 studies were available, respectively). The influence of individual studies on the overall ES was also investigated using a *leave-one-out* sensitivity analyses [30].

To examine the possibility of publication bias affecting the results, the Eggers' t-test was conducted for meta-analyses with ≥10 studies, as per the Cochrane Collaboration Handbook [31]. Similarly, funnel plots of effect sizes for each metabolite with ≥10 studies were generated. A Duval and Tweedie's 'trim-and-fill' analysis was applied to the random-effects models to re-calculate the pooled effect size to account for any studies which may introduce publication bias. The significance of heterogeneity among studies was examined by the Q statistics, and the I^2 was then used to assess the level that the variance among studies could be accounted for by potential systematic factors. We performed a meta-analysis only when at least three studies for a given metabolite were available.

Results

The search strategy resulted in 6519 de-duplicated studies that were screened. A total of 101 studies, comprising 128 comparisons (k), 10,912 participants (5856 with MDD, BD or SZ, and 5056 controls) were included (Fig. 1) [32–126]. Sample sizes for each study had a median of 58 participants (range 15–1101). Eighty-six comparisons measured the metabolites in plasma, while 42 measured metabolites in serum. The median age of participants was 25 years (range 25–67). We reported the results according to the different disorders investigated.

Major depressive disorder

A total of 59 studies, comprising 77 comparisons with 6819 participants ($n = 3896$ with MDD and $n = 2923$ healthy controls), were included [32, 33, 35, 36, 41–47, 50, 51, 56–59, 61, 62, 64, 65, 67–69, 72–86, 90, 91, 93, 96, 98, 103, 104, 106, 108, 110, 111, 113, 115, 117, 121–126]. Of the comparisons that reported medication details (k = 62; 80%), most comparisons (k = 52, 84%) included participants that were either treatment naive or had been removed from medication prior to study commencement. Characteristics of the studies and details regarding the metabolites assessed in each study were reported in Table 1.

Tryptophan ($g = -0.51$, 95% CI = −0.63 to −0.39, $p =$ <0.001, $I^2 = 76\%$, $k = 57$, $n = 7252$), kynurenine ($g =$ −0.26, 95% CI = −0.35 to −0.16, $p =$ <0.001, $I^2 = 44\%$, $k = 26$, $n = 4790$), and kynurenic acid ($g = -0.37$, 95% CI = −0.52 to −0.21, $p = 0.001$, $I^2 = 60\%$, $k = 18$, $n =$ 1959) were significantly lower in people with MDD than in healthy controls. There were no significant differences in quinolinic acid ($g = -0.03$, 95% CI = −0.28 to 0.22, $p =$ 0.80, $I^2 = 71\%$, $k = 9$, $n = 991$) and 3-hydroxykynurenine ($g = 0.04$, 95% CI = −0.11 to 0.18, $p = 0.63$, $I^2 = 0\%$, $k =$ 6, $n = 757$) between people with MDD and healthy controls (Fig. 2a, Supplementary Figs. 1–9).

Ratios of kynurenic acid to kynurenine ($g = -0.39$, 95% CI = −0.73 to −0.04, $p = 0.03$, $I^2 = 82\%$, $k = 6$, $n = 859$), kynurenic acid to quinolinic acid ($g = -0.54$, 95% CI = −0.82 to −0.27, $p =$ <0.001, $I^2 = 59\%$, $k = 5$, $n = 633$) and kynurenic acid to 3-hydroxykynurenine ($g = -0.42$, 95% CI = −0.63 to −0.21, $p =$ <0.001, $I^2 = 23\%$, $k = 4$, $n =$ 577) were significantly lower in people with MDD compared to healthy controls. There was no statistically significant difference in the kynurenine to tryptophan ratio

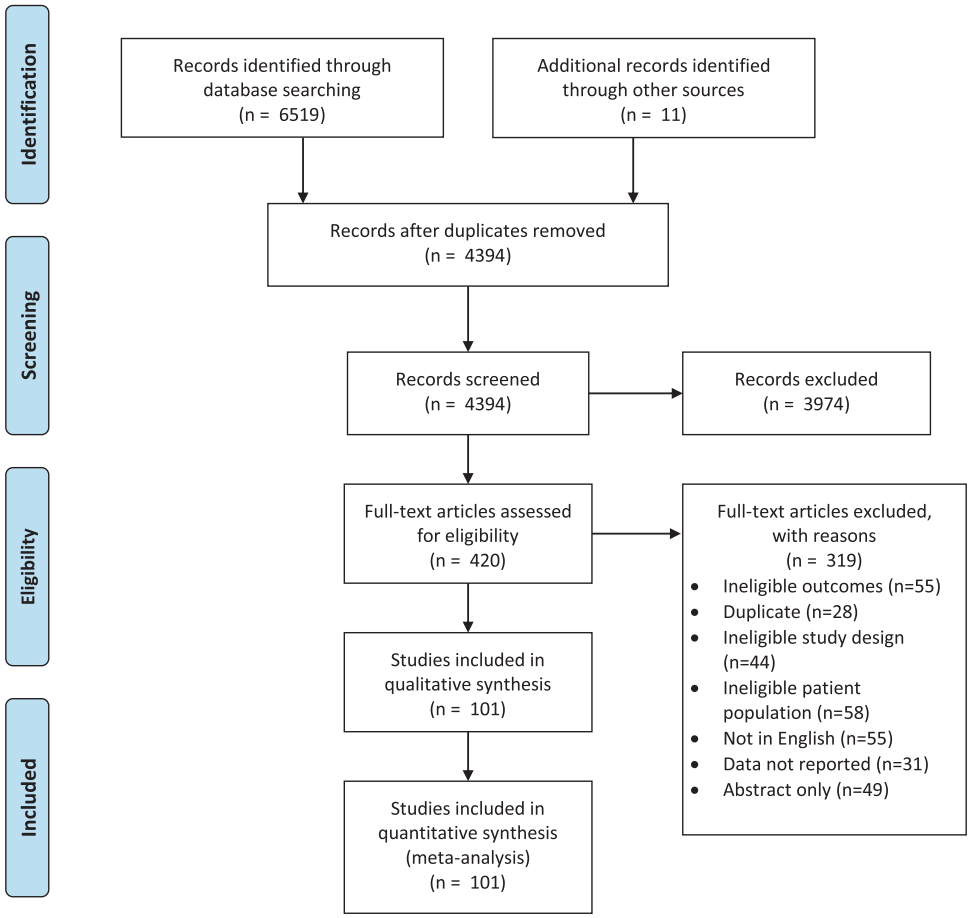

Fig. 1 PRISMA flow diagram of the included studies. In total, 101 studies were included.

($g = 0.10$, 95% CI = −0.05 to 0.25, $p = 0.18$, $I^2 = 71\%$, $k = 17$, $n = 3997$) (Figs. 2a and 3).

In order to verify the consistency of our results, we conducted several sensitivity and sub-groups analyses. In a sensitivity analyses of sample source (plasma vs. serum), the one study that assessed kynurenic acid to kynurenine ratio in plasma reported significantly lower levels in people with MDD compared to controls, while studies ($n = 5$) that assessed serum samples reported no significant differences. There was no difference in effect or heterogeneity for all other metabolites. Meta-regression analyses based on age and sex (% male sex) were also not significant (Supplementary Table 1).

In the *leave-one-out* analyses, the removal of Umehara et al. [117] resulted in a significant difference in kynurenine to tryptophan ratio whereby people with MDD had a significantly higher ratio compared to healthy controls ($g = 0.15$, 95% CI = 0.007 to 0.291, $p = 0.04$, $I^2 = 66$, $k = 11$, $n = 3931$). No other metabolites or ratios were influenced by removing any individual study. Funnel plots are included in the Supplementary Material (Supplementary Figs. 10–13). While Egger's regression test for kynurenic acid ($p = 0.44$) and for kynurenine to tryptophan ratio ($p = 0.15$) had no indication of publication bias, possible publication bias was detected for tryptophan ($p = <0.001$) and kynurenine ($p = 0.002$). However, the effect sizes of these metabolites were unaffected by a random effects trim-and-fill analysis.

Bipolar disorder

A total of 14 studies, comprising 15 unique comparisons and 1202 participants ($n = 497$ BD, $n = 705$ healthy controls), were included in these meta-analyses [36, 38, 41, 60, 72, 73, 87, 89, 94, 95, 102, 105, 108, 124]. Of the comparisons that reported medication details (k = 10; 66%), five comparisons (50%) included participants that were either treatment naive or had been removed from medication prior to study commencement while the other half had at least 50% of participants receiving medication. Details of the studies and metabolites assessed can be found in Table 2.

Tryptophan ($g = -0.56$, 95% CI = −0.76 to −0.35, $p = <0.001$, $I^2 = 48$, $k = 12$, $n = 851$), kynurenic acid ($g = -0.44$, 95% CI = −0.65 to −0.24, $p = <0.001$, $I^2 = 33\%$, $k = 7$, $n = 615$) and kynurenic acid to quinolinic acid ($g = -0.44$, 95% CI = −0.67 to −0.21, $p = <0.0001$, $I^2 = 62\%$, $k = 3$, $n = 299$) were significantly lower in people

Table 1 Characteristics of the studies for major depressive disorder.

Study name	Sample size	Study characteristics	Medical Hx	Serum / plasma	Metabolites extracted and effect direction
Anderson et al. [32]	Total: 62 Case: 31 Control: 31	Country: United Kingdom Mean age: 33.3 Sex (%Male): 52%	%Medicated: None	Plasma	TRYP: ↓
Baranyi et al. [33]	Total: 119 Case: 71 Control: 48	Country: Austria Mean age: 47.6 Sex (%Male): 65%	%Medicated: Unclear	Plasma	TRYP: ↓ KYN: NS KYNA: NS QUIN: NS KYN/TRYP: NS
Bhagwagar et al. [35]	Total: 31 Case: 11 Control: 20	Country: United Kingdom Mean age: 44.0 Sex (%Male): 59%	%Medicated: None	Plasma	TRYP: NS
Brundin et al. [36]	Total: 44 Case: 15 Control: 29	Country: Sweden Mean age: 41.5 Sex (%Male): 28%	%Medicated: None	Plasma	QUIN: NS
Chiaroni et al. [41]	Total: 79 Group 1: 21 Group 2: 25 Control: 33	Country: France/Switzerland Mean age: 49.8 Sex (%Male): 35.5%	%Medicated: None	Plasma	TRYP: ↓
Cho et al. [42]	Total: 226 Case Group 1: 26 Case Group 2: 68 Control: 132	Country: United States of America Mean age: 33.5 Sex (%Male): 31.5%	%Medicated: None	Serum	TRYP:↓ KYN: NS KYNA: NS 3-HK: NS QUIN: NS KYN/TRYP: NS KYNA/QA: ↓ KYNA/3HK: ↓
Coppen et al. [43]	Total: 72 Case Group 1: 24 Case Group 2: 11 Case Group 3: 11 Control: 26	Country: United Kingdom Mean age: 53.7 Sex (%Male): 0%	%Medicated: Mixed	Plasma	TRYP:↓
Cowen et al. [44]	Total: 24 Case: 12 Control: 12	Country: United Kingdom Mean age: 36.4 Sex (%Male): 50%	%Medicated: None	Plasma	TRYP:↓
Czermak et al. [45]	Total: 54 Case: 28 Control: 26	Country: United States of America Mean age: 36.7 Sex (%Male): 30%	%Medicated: None	Plasma	TRYP: NS
Dahl et al. [46]	Total: 84 Case: 49 - 50 Control: 33-34	Country: Norway Mean age: 39.2 Sex (%Male): 35%	%Medicated: None		TRYP: NS KYNA: NS QUIN: NS KYN/KYNA: NS KYN/TRYP: NS KYN: NS:
DeMyer et al. [47]	Total: 24 Case: 15 Control: 9	Country: United States of America Mean age: 33.4 Sex (%Male): 33%	%Medicated: None	Plasma	TRYP:↓
Doolin et al. [50]	Total: 111 Case: 74 Control: 37	Country: Ireland Mean age: 31.9 Sex (%Male): 43%	%Medicated: >50%	Plasma	TRYP:↓ KYN: NS KYNA:↓ QUIN: NS
Ebesunun et al. [51]	Total: 60 Case: 30 Control: 30	Country: Nigeria Mean age: 40.2 Sex (%Male): 30%	%Medicated: Unclear	Plasma	TRYP: NS
Guicheney et al. [56]	Total: 45 Case: 31 Control: 14	Country: France Mean age: 51.9 Sex (%Male): 0%	%Medicated: None	Plasma	TRYP: NS
Hayward et al. [57]	Total: 24 Case: 12 Control: 12	Country: United Kingdom Mean age: 39.3 Sex (%Male): 58%	%Medicated: None	Plasma	TRYP: NS
	Total: 24 Case: 12 Control: 12	Country: United Kingdom Mean age: 39.3 Sex (%Male): 58%	%Medicated: None	Plasma	TRYP: NS
Healy et al. [58]	Total: 44 Case Group 1: 6 Case Group 2: 18 Control: 20	Country: Ireland Mean age: 35.5 Sex (%Male): 36	%Medicated: None	Plasma	TRYP: NS
Hennings et al. [59]	Total: 86 Case: 38 Control: 48	Country: Germany Mean age: 34.3 Sex (%Male): 26%	%Medicated:<50%	Serum	TRYP: NS KYN: ↓

Table 1 (continued)

Study name	Sample size	Study characteristics	Medical Hx	Serum / plasma	Metabolites extracted and effect direction
Hoekstra et al. [61]	Total: 49 Case: 20 Control: 29	Country: Netherlands Mean age: 44.5 Sex (%Male): 45%	%Medicated: None	Plasma	TRYP:↓
Hu et al. [62]	Total: 80 Case: 54 Control: 26	Country: China Mean age: Not reported Sex (%Male): Not reported	%Medicated: Unclear	Serum	TRYP: ↓ KYN: ↓ KYNA: NS
Joseph et al. [64]	Total: 24 Case: 16 Control: 8	Country: United States of America Mean age: 42.8 Sex (%Male): 38%	%Medicated: None	Plasma	TRYP:↓
Karege et al. [65]	Total: 50 Case: 30 Control: 20	Country: Switzerland Mean age: 47.0 Sex (%Male): 42%	%Medicated: None	Plasma	TRYP:↓
Krause et al. [67]	Total: 80 Case: 37 Control: 43	Country: Germany Mean age: 34.6 Sex (%Male): 29%	%Medicated: <50%	Serum	TRYP: NS KYN: NS KYNA: NS 3-HK: NS KYNA/KYN: NS KYN/TRYP: NS
Krause et al. [68]	Total: 52 Case: 32 Control: 20	Country: United Kingdom Mean age: 42.3 Sex (%Male): 63%	%Medicated: None	Serum	KYN: ↓ KYNA: ↓ KYNA/QA:↓
Kuwano et al. [69]	Total: 34 Case: 15 Control: 19	Country: Japan Mean age: 30.2 Sex (%Male): 56%	%Medicated: None	Plasma	TRYP:↓ KYN: ↓ KYNA: NS 3-HK: NS KYN/TRYP: NS
Liu et al. [72]	Total: 56 Case: 33 Control: 23	Country: China Mean age: 28.8 Sex (%Male): 41%	%Medicated: Unclear	Plasma	TRYP:NS KYN: NS KYNA: ↓ QUIN: ↓ KYNA/KYN: ↓ KYN/TRYP: NS KYNA/QA: ↓
Lucca et al. [73]	Total: 48 Case: 19 Control: 29	Country: Italy Mean age: 42.5 Sex (%Male): 44%	%Medicated: None	Plasma	TRYP:↓
Maes et al. [76]	Total: 66 Case Group 1: 13 Case Group 2: 22 Case Group 3: 15 Control: 16	Country: Belgium Mean age: 45.7 Sex (%Male): 45.33%	%Medicated: None	Serum	TRYP:↓
Maes et al. [77]	Total: 32 Case Group 1: 10 Case Group 2: 7 Case Group 3: 7 Control: 8	Country: Belgium Mean age: 45.3 Sex (%Male): 0%	%Medicated: None	Plasma	TRYP:↓
Maes et al. [74]	Total: 173 Case Group 1: 35 Case Group 2: 41 Case Group 3: 47 Control: 50	Country: Belgium Mean age: 43.7 Sex (%Male): 44%	%Medicated: None	Plasma	TRYP:↓
Maes et al. [79]	Total: 66 Case Group 1: 9 Case Group 2: 12 Case Group 3: 21 Control: 24	Country: Belgium Mean age: 45.7 Sex (%Male): 36.67%	%Medicated: None	Serum	TRYP:↓
Maes et al. [78]	Total: 50 Case: 35 Control: 15	Country: Belgium Mean age: 49.1 Sex (%Male): 58%	%Medicated: None	Serum	TRYP:↓
Maes et al. [75]	Total: 71 Case: 36 Control: 35	Country: Germany Mean age: 39.95 Sex (%Male): 42	%Medicated: None	Plasma	TRYP:↓ KYN: NS KYNA: NS KYN/KYNA: NS KYN/TRYP: NS
Mauri et al. [80]	Total: 57 Case: 29 Control: 28	Country: Italy Mean age: 44.9 Sex (%Male): 54%	%Medicated: None	Plasma	TRYP: NS

Table 1 (continued)

Study name	Sample size	Study characteristics	Medical Hx	Serum / plasma	Metabolites extracted and effect direction
Meier et al. [81]	Total: 164 Case: 73 Control: 91	Country: United States of America Mean age: 33.0 Sex (%Male): 31%	%Medicated: None	Serum	TRYP:↓ KYN: NS KYNA: NS 3-HK: NS QUIN: NS KYN/TRYP: ↑ KYNA/QA: ↓ KYNA/3HK:↓
Moaddel et al. [82]	Total: 54 Case: 29 Control: 25	Country: United States of America Age (Range): 18-65 Sex (%Male): 39%	%Medicated: None	Plasma	TRYP:↓ KYN: NS KYN/TRYP:↑
Moller et al. [84]	Total: 81 Case: 26 Control: 55	Country: Denmark Mean age: 45.0 Sex (%Male): 30%	%Medicated: None	Plasma	TRYP: NS
Moller et al. [83]	Total: 86 Case Group 1: 14 Case Group 2: 12 Control: 60	Country: Denmark Mean age: 50.5 Sex (%Male): 0%	%Medicated: Unclear	Plasma	TRYP: NS
Moreno et al. [86]	Total: 60 Case: 30 Control: 30	Country: Mexico Mean age: 32.4 Sex (%Male): 20%	%Medicated: None	Plasma	TRYP:↓
Moreno et al. [85]	Total: 24 Case: 12 Control: 12	Country: United States of America Mean age: 47.3 Sex (%Male): 33%	%Medicated: None	Plasma	TRYP: NS
Myint et al. [89]	Total: 247 Case: 58 Control: 189	Country: South Korea Mean age: 38.6 Sex (%Male): 49%	%Medicated: Unclear	Plasma	TRYP: NS KYN: NS KYNA: ↓
Ogawa et al. [91]	Total: 364 Case: 147 Control: 217	Country: Japan Mean age: 41.7 Sex (%Male): 48%	%Medicated: Unclear	Plasma	TRYP:↓
	Total: 116 Case: 51 Control: 65	Country: Japan Mean age: 43.8 Sex (%Male): 42%	%Medicated: Unclear	Plasma	TRYP: NS
Pan et al. [93]	Total: 100 Case: 50 Control: 50	Country: China Mean age: 37.6 Sex (%Male): 48%	%Medicated: None	Plasma	TRYP:↓ KYN: ↓ 3-HK: NS
Porter et al. [96]	Total: 40 Case: 20 Control: 20	Country: United Kingdom Mean age: 33.5 Sex (%Male): 48%	%Medicated: None	Plasma	TRYP: NS
Quintana et al. [98]	Total: 50 Case: 25 Control: 25	Country: Spain Mean age: 54.0 Sex (%Male): 20%	%Medicated: None	Plasma	TRYP: NS
Rief et al. [103]	Total: 72 Case: 36 Control: 36	Country: Germany Mean age: 40.1 Sex (%Male): 43%	%Medicated: None	Plasma	TRYP: ↓
Roiser et al. [104]	Total: 45 Case: 23 Control: 22	Country: United States of America Mean age: 31.5 Sex (%Male): 29%	%Medicated: None	Plasma	TRYP: NS
Schwieler et al. [106]	Total: 32 Case: 18 Control: 14	Country: Sweden Mean age: 32.5 Sex (%Male): 81%	%Medicated: 100%	Plasma	KYNA:↓
Shaw et al. [108]	Total: 82 Case Group 1: 37 Case Group 2: 9 Control: 36	Country: United Kingdom Mean age: Not reported Sex (%Male): 43%	%Medicated: Unclear	Plasma	TRYP:↓
Song et al. [110]	Total: 20 Case: 6 Control: 14	Country: Belgium Mean age: 47.9 Sex (%Male): 45%	%Medicated: None	Plasma	TRYP: NS
Sorgdrager et al. [111]	Total: 1726 Case Group 1: 695 Case Group 2: 625 Control: 406	Country: The Netherlands Mean age: 42.8 Sex (%Male): 35.5%	%Medicated: Unclear	Serum	TRYP: NS KYN: NS KYN/TRYP: NS
Sublette et al. [113]	Total: 61 Case: 30 Control: 31	Country: United States of America Mean age: 36.7 Sex (%Male): 43%	%Medicated: >50%	Plasma	TRYP: NS KYN: NS KYN/TRYP:↑
Teraishi et al. [115]	Total: 42 Case: 18 Control: 24	Country: Japan Mean age: 42.5 Sex (%Male): 47%	%Medicated: Unclear	Plasma	TRYP: NS

Table 1 (continued)

Study name	Sample size	Study characteristics	Medical Hx	Serum / plasma	Metabolites extracted and effect direction
Umehara et al. [117]	Total: 66 Case: 33 Control: 33	Country: Japan Mean age: 40.1 Sex (%Male): 30%	%Medicated: None	Plasma	KYN: ↓ KYN/TRYP: NS
Wood et al. [121]	Total: 33 Case: 17 Control: 16	Country: United Kingdom Mean age: 56.1 Sex (%Male): 0%	%Medicated: None	Plasma	KYN: NS
	Total: 24 Case: 10 Control: 14	Country: United Kingdom Mean age: 54.5 Sex (%Male): 100%	%Medicated: None	Plasma	KYN: NS
Wu et al. [123]	Total: 200 Case: 71 Control: 129	Country: China Mean age: 66.8 Sex (%Male): 31%	%Medicated: >50%	Serum	TRYP:↓ KYN: ↓ KYNA: NS KYNA/KYN: NS KYN/TRYP:↑
Wu et al. [123]	Total: 385 Case: 170 Control: 135	Country: China Mean age: 66.8 Sex (%Male): 26%	%Medicated: >50%	Serum	TRYP:↓ KYN: ↓ KYN/KYNA: NS KYN/TRYP: NS
Wurfel et al. [124]	Total: 127 Case: 35 Control: 92	Country: United States of America Mean age: 35.5 Sex (%Male): 42%	%Medicated: Unclear	Serum	TRYP: NS KYN: NS KYNA: NS 3-HK: NS QUIN: NS KYN/TRYP: NS KYNA/QA: ↓ KYNA/3HK: NS
Young et al. [125]	Total: 60 Case: 35 Control: 25	Country: United States of America Mean age: 36.2 Sex (%Male): 39%	%Medicated: None	Serum	TRYP: NS KYN: NS KYNA: ↓ 3-HK: NS QUIN: ↑ KYNA/QA: ↓ KYNA/3HK: ↓
Zhou et al. [126]	Total: 117 Case: 76 Control: 41	Country: China Mean age: 31.1 Sex (%Male): 100%	%Medicated: >50%	Serum	TRYP:↓ KYN: NS KYNA: ↓ KYNA/KYN: ↓ KYN/TRYP:↑
	Total: 101 Case: 70 Control: 31	Country: China Mean age: 35.7 Sex (%Male): 0%	%Medicated: >50%	Serum	TRYP:↓ KYN: NS KYNA: ↓ KYNA/KYN: ↓ KYN/TRYP:↑

↑: increased in people with depression, ↓: decreased in people with depression, *NS* non-significant difference between healthy controls and people with depression, *Medical Hx* Medical History, *TRYP* Tryptophan, *KYN* Kynurenine, *KYNA* Kynurenic Acid, *3-HK* 3-Hydroxy Kynurenine, *QUIN* Quinolinic Acid, *KYN/KYNA* Kynurenine/Kynurenic Acid Ratio, *KYN/TRYP* Kynurenine/Tryptophan Ratio, *KYNA/QA* Kynurenic Acid/ Quinolinic Acid Ratio, *KYNA/3HK* Kynurenic Acid/: 3-Hydroxy Kynurenine Ratio.

with BD compared to healthy controls. There were no statistically significant differences in quinolinic acid ($g = -0.40$, 95% CI = −1.01 to 0.20, $p = 0.19$, $I^2 = 88\%$, $k = 5$, $n = 416$), kynurenine ($g = -0.12$, 95% CI = −0.43 to 0.19, $p = 0.46$, $I^2 = 79\%$, $k = 9$, $n = 898$), 3-hydroxykynurenine ($g = 0.06$, 95% CI = −0.23 to 0.34, $I^2 = 62\%$, $p = 0.70$, $k = 6$, $n = 572$), and kynurenine to tryptophan ratio ($g = 0.11$, 95% CI = −0.16 to 0.38, $p = 0.41$, $I^2 = 65\%$, $k = 7$, $n = 737$) (Figs. 2b and 3, and Supplementary Figs. 14–20).

In a series of sub-group analyses, studies measuring kynurenine in plasma reported significantly lower levels in people with BD ($g = -0.34$, 95% CI = −0.62 to −0.061, $p = 0.02$), while those measuring kynurenine in serum reported no significant difference between people with BD and healthy controls ($g = -0.01$, 95% CI = −0.41 to 0.39, $p = 0.96$; Supplementary Table 2).

Meta-regression analyses showed that mean age was positively associated with higher levels of kynurenic acid ($p = 0.04$) and kynurenine to tryptophan ratio ($p < 0.0001$), as well as lower levels of tryptophan ($p = 0.03$), in people with BD compared to healthy controls. Sub-group analysis by biological source (plasma or serum) greatly decreased heterogeneity in studies that measured kynurenine in plasma ($I^2 = 0\%$) and tryptophan when measured in serum ($I^2 = 0\%$). Planned sub-group analysis based on bipolar phase (depressed, euthymic, manic) showed some differences according to mood state. Tryptophan and kynurenic acid were decreased in acute states (i.e., mania and depression)

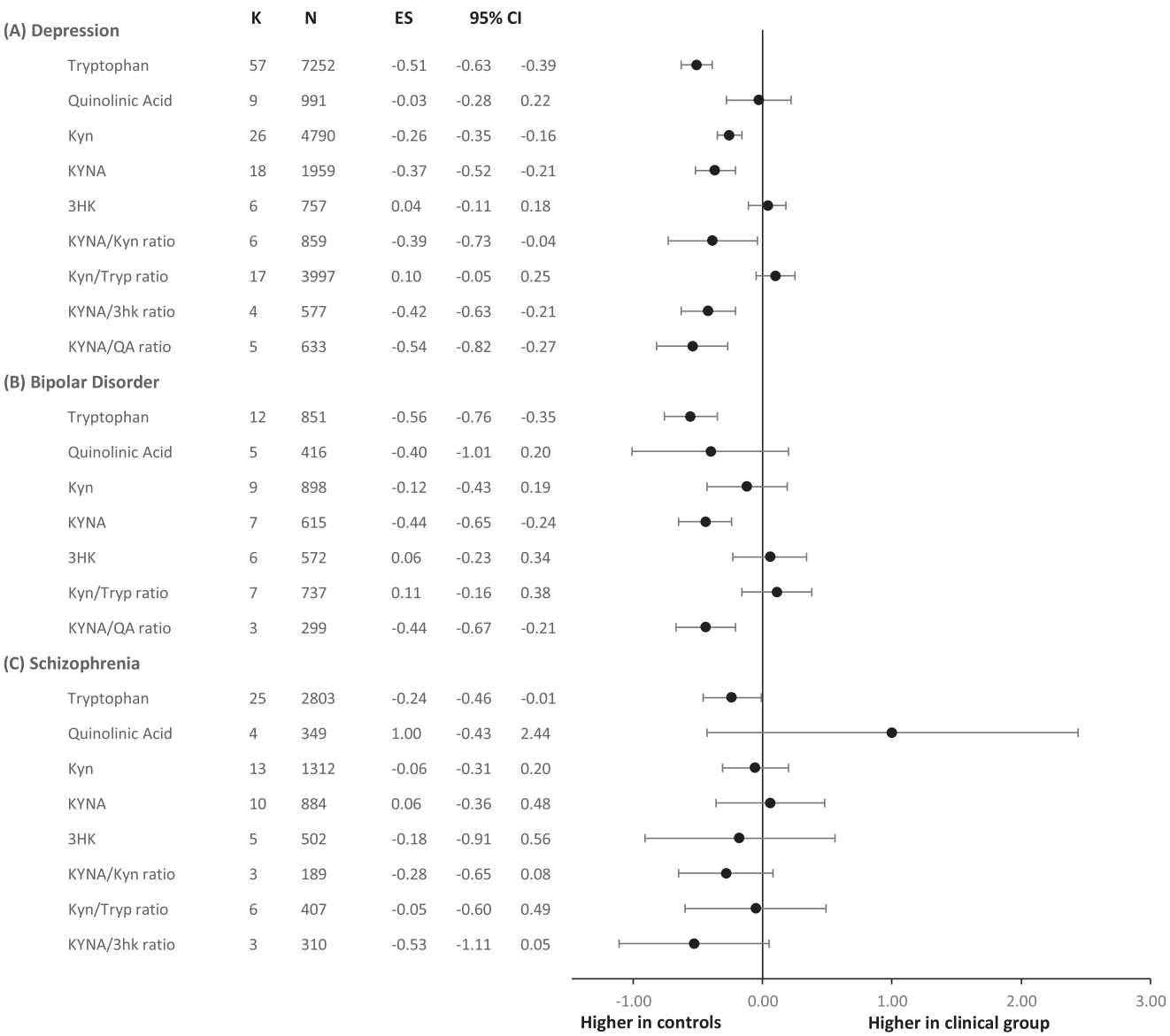

Fig. 2 Forest plots with the summary effect size (Hedge's g) of kynurenine metabolites in people with Major Depressive Disorder, Bipolar Disorder, or Schizophrenia compared to healthy controls. **a)** Major depressive disorder compared to healthy controls; **b)** Bipolar disorder compared to healthy controls; **c)** Schizophrenia compared to healthy controls. TRYP Tryptophan, KYN Kynurenine, KYNA Kynurenic Acid, 3-HK 3-Hydroxykynurenine, QUIN Quinolinic Acid, KYNA/KYN Kynurenic Acid/Kynurenine Ratio, KYN/TRYP Kynurenine/Tryptophan Ratio, KYNA/QA Kynurenic Acid/Quinolinic Acid Ratio, KYNA/3HK Kynurenic Acid/3-Hydroxykynurenine Ratio.

but not in euthymia; kynurenine and quinolinic acid were decreased only during a depressive state; 3-hydroxykynurenine and kynurenine to tryptophan ratio were increased only in euthymia. However, the small number of studies included in each of these sub-group analyses should be noted. Regarding sex, the % of male sex in the studies was associated with a lower ratio of kynurenine to tryptophan ratio in people with BD compared to healthy controls. No other significant results were reported and due to the limited number of studies, sub-group analyses were not conducted for all other metabolites (Supplementary Table 2).

In the *leave–one-out* analyses, the removal of the study by Reininghaus et al. [102], which was the only study that reported increased levels of kynurenine in BD, resulted in significant difference in kynurenine between people with BD and healthy controls, with a pooled ES showing decreased kynurenine levels in BD compared to controls ($g = -0.23$, 95% CI $= -0.38$ to -0.071, $p = 0.04$). No other metabolites or ratios were influenced by removing any

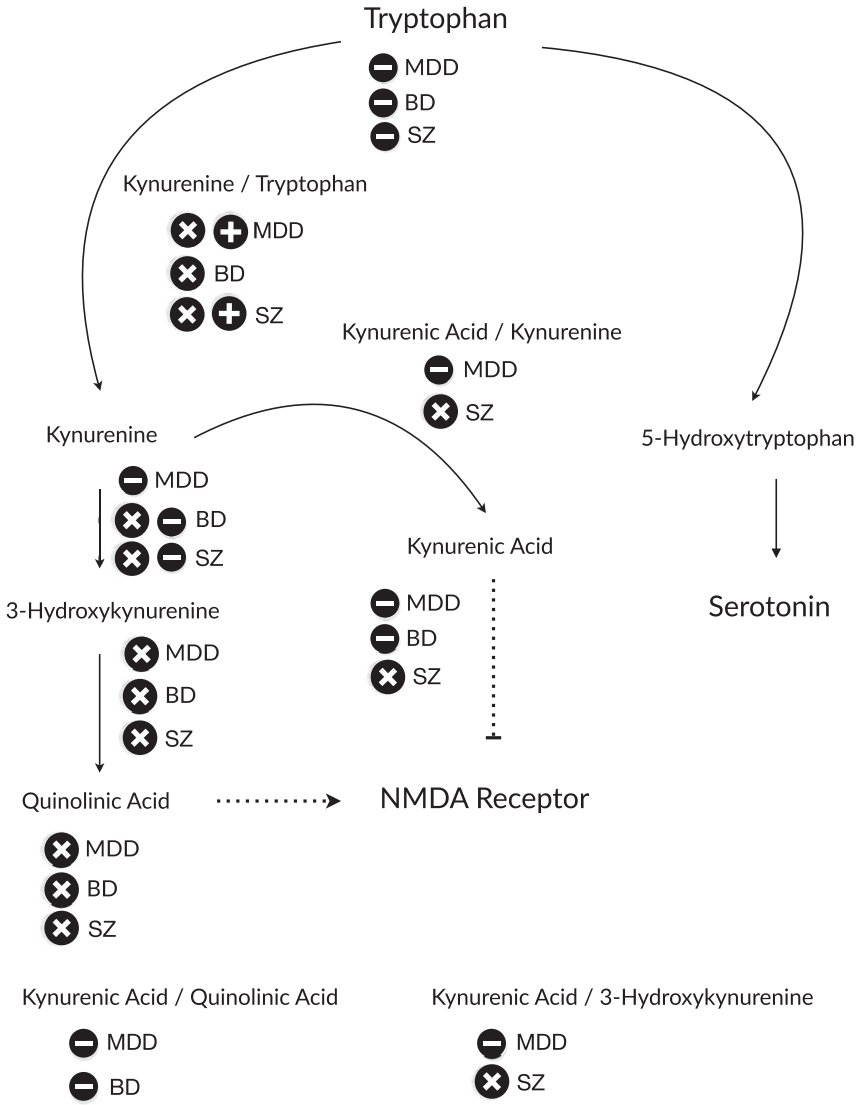

Fig. 3 Summary representation of the altered metabolites in the kynurenine pathway in Major Depressive Disorder, Bipolar Disorder, or Schizophrenia. Minus sign (−) denotes decreased levels of metabolites or ratios in the disorder compared to healthy controls; plus sign (+) denotes increased levels of metabolites or ratios in the disorder compared to healthy controls; and an X denotes a non-significant difference in the disorder compared to healthy controls. When a given disorder was not included in a given metabolite or ratio, it denotes that the given metabolite or ratio was not meta-analysed for that given disorder. When a given metabolite is coded with both minus or plus sign after an X, it denotes that a planned sub-group analysis found that metabolite altered.

other individual study. Egger's regression test for tryptophan did not detect possible publication bias (Supplementary Fig. 21). Trim-and-fill analysis resulted in no change to the original effect size (adjusted effect size = −0.79, original effect size = −0.73).

Schizophrenia

Thirty studies, comprising 36 unique comparisons and 2891 participants ($n = 1463$ with SZ, $n = 1428$ healthy controls) were included in the meta-analyses [34, 36, 37, 39, 40, 48, 49, 52–55, 63, 66, 70, 71, 88, 92, 97, 99–101, 107, 109, 112, 114, 116, 118–120, 124]. Similar to MDD, of the comparisons that reported medication details (k = 33; 92%), most comparisons (k = 19, 58%) included participants that were either treatment naive or had been removed from medication prior to study commencement. Characteristics of these studies are in Table 3.

Tryptophan ($g = -0.24$, 95% CI = −0.46 to −0.01, $p = 0.04$, $I^2 = 85\%$, $k = 25$, $n = 2803$) was significantly lower in people with SZ compared to healthy controls. There were no significant differences in kynurenine ($g = -0.06$, 95% CI = −0.31 to 0.20, $p = 0.65$, $I^2 = 76\%$, $k = 13$, $n = 1312$), kynurenic acid ($g = 0.06$, 95% CI = −0.36 to 0.48, $p = 0.78$, $I^2 = 87\%$, $k = 10$, $n = 884$), 3-hydroxykynurenine ($g = -0.18$, 95% CI = −0.91 to 0.56, $p = 0.64$, $I^2 = 93\%$, $k = 5$, $n = 502$), quinolinic acid ($g = 1.00$, 95% CI = −0.43 to 2.44, $p = 0.17$, $I^2 = 95\%$, $k = 4$, $n = 349$), kynurenic acid to 3-hydroxykynurenine ratio ($g = -0.53$, 95% CI = −1.11 to 0.05, $I^2 = 81\%$, $p = 0.07$, $k = 3$, $n = 310$), kynurenic acid to kynurenine ratio ($g = -0.28$, 95% CI = −0.65 to 0.08, $p = 0.13$, $I^2 = 30\%$, $k = 3$, $n = 189$), and kynurenine to tryptophan ratio ($g = -0.05$,

Table 2 Characteristics of the studies for bipolar disorder.

Study name	Sample size	Study characteristics	Medical Hx	Serum / plasma	Metabolites measured and effect direction
Brundin et al. [36]	Total: 50 Case: 21 Control: 29	Country: Sweden Mean age: 38.8 Sex (%Male): 0%	Phase: Unclear %Medicated: None	Plasma	QUIN: NS
Castillo et al. [38]	Total: 67 Case: 43 Control: 24	Country: United State of America Mean age: 47.5 Sex (%Male): 46%	Phase: Depressive %Medicated: Unclear	Serum	QUIN: ↓
Chiaroni et al. [41]	Total: 51 Case: 18 Control: 33	Country: France/ Switzerland Mean age: 48.9 Sex (%Male): 41%	Phase: Depressive %Medicated: None	Plasma	TRYP: ↓
Hoekstra et al. [60]	Total: 40 Case: 20 Control: 20	Country: The Netherlands Mean age: 50.2 Sex (%Male): 70%	Phase: Manic %Medicated: All	Plasma	TRYP:↓
Liu et al. [72]	Total: 43 Case: 20 Control: 23	Country: China Mean age: 29.9 Sex (%Male): 46%	Phase: Depressive %Medicated: Unclear	Plasma	TRYP: NS KYN: NS KYNA: ↓ QUIN: ↓ KYN/TRYP: NS KYNA/QA: NS
Lucca et al. [46]	Total: 38 Case: 9 Control: 29	Country: Italy Mean age: 42.0 Sex (%Male): 48%	Phase: Depressive %Medicated: None	Plasma	TRYP: NS
Mukherjee et al. [87]	Total: 49 Case: 21 Control: 28	Country: United States of America Mean age: 33.8 Sex (%Male): 48%	Phase: Mixed %Medicated: All	Plasma	TRYP: ↓ KYN: NS KYN/TRYP: NS
Myint et al. [89]	Total: 119 Case: 39 Control: 80	Country: Korea Mean age: 38.3 Sex (%Male): 44%	Phase: Manic %Medicated: None	Plasma	TRYP: ↓ KYN: NS KYNA: ↓ 3-HK: NS KYN/TRYP: NS
Platzer et al. [94]	Total: 83 Case: 26 Control: 57	Country: Austria Mean age: 43.2 Sex (%Male): 0%	Phase: Euthymic %Medicated: Unclear	Serum	TRYP: NS KYN: NS KYNA: NS 3-HK: ↑
	Total: 78 Case: 42 Control: 36	Country: Austria Mean age: 40.9 Sex (%Male): 100%	Phase: Euthymic %Medicated: Unclear	Serum	TRYP: ↓ KYN: NS KYNA: NS 3-HK: NS
Poletti et al. [95]	Total: 36 Case: 22 Control: 14	Country: Italy Mean age: 36.9 Sex (%Male): 40%	Phase: Depressive %Medicated: >50%	Serum	TRYP: NS KYN: NS KYNA: NS 3-HK: NS KYN/TRYP: NS
Reininghaus et al. [102]	Total: 234 Case: 78 Control: 156	Country: Austria Mean age: 40.5 Sex (%Male): 0%	Phase: Euthymic %Medicated: >50%	Serum	KYN: ↑ KYN/TRYP: ↑
Savitz et al. [105]	Total: 111 Case: 63 Control: 48	Country: United States of America Mean age: 35.7 Sex (%Male): 29%	Phase: Mixed %Medicated: >50%	Serum	TRYP: ↓ KYN: NS KYNA: NS 3-HK: NS QUIN: NS KYN/TRYP: NS KYNA/QA: NS
Shaw et al. [108]	Total: 58 Case: 22 Control: 36	Country: United Kingdom Mean age: Not reported Sex (%Male): 46%	Phase: Mixed %Medicated: Not reported	Plasma	TRYP: NS
Wurfel et al. [124]	Total: 145 Case: 53 Control: 92	Country: United States of America Mean age: 36.2 Sex (%Male): 33%	Phase: Mixed %Medicated: Unclear	Serum	TRYP: ↓ KYN: NS KYNA: ↓ 3-HK: ↓ QUIN: NS KYN/TRYP: NS KYNA/QA: ↓

↑: increased in people with Bipolar Disorder, ↓: decreased in people with Bipolar Disorder, *NS* non-significant difference between healthy controls and people with bipolar disorder, *Medical Hx* Medical History, *Dx* Diagnosis, *TRYP* Tryptophan, *KYN* Kynurenine, *KYNA* Kynurenic Acid, 3-HK: 3-Hydroxy Kynurenine, *QUIN* Quinolinic Acid, *KYNA/KYN* Kynurenic Acid/Kynurenine Ratio, *KYN/TRYP* Kynurenine/Tryptophan Ratio, *KYNA/QA* Kynurenic Acid/Quinolinic Acid Ratio, *KYNA/3HK* Kynurenic Acid/3-Hydroxy Kynurenine Ratio.

Table 3 Characteristics of the studies for schizophrenia.

Study name	Sample size	Study characteristics	Medical Hx	Serum / Plasma	Metabolites measured and effect direction
Barry et al. [34]	Total: 70 Case: 34 Control: 36	Country: Ireland Mean age: 35.5 Sex (%Male): 66%	%Medicated: >50% Dx: Schizophrenia and schizoaffective	Plasma	TRYP: NS KYN: NS KYNA: NS KYNA/KYN: NS KYN/TRYP: NS
Brundin et al. [36]	Total: 32 Case: 3 Control: 29	Country: Sweden Mean age: 38.5 Sex (%Male): Not reported	%Medicated: 0% Dx: Psychotic disorder and suicide attempter	Plasma	QUIN: NS
Cao et al. [37]	Total: 383 Case: 208 Control: 175	Country: China Mean age: 38.6 Sex (%Male): 67%	%Medicated: 0% Dx: Schizophrenia	Plasma	TRYP: ↓ KYN: ↓
Carl et al. [137]	Total: 26 Case: 13 Control: 13	Country: United States of America Mean age: 38.2 Sex (%Male): 100%	%Medicated: >50% Dx: Schizophrenia	Plasma	TRYP: NS
Chiappelli et al. [40]	Total: 75 Case: 37 Control: 38	Country: United States of America Mean age: 39.5 Sex (%Male): 71%	%Medicated: >50% Dx: Schizophrenia and Schizoaffective	Plasma	TRYP: ↓ KYN: NS KYN/TRYP: ↑
Chiappelli et al. [39]	Total: 210 Case: 106 Control: 104	Country: United States of America Mean age: 35.9 Sex (%Male): 61%	%Medicated: >50% Dx: Schizophrenia and Schizoaffective	Plasma	KYN: NS KYNA: ↓
Domingues et al. [49]	Total: 73 Case Group 1: 27 Case Group 2: 8 Control: 38	Country: Brazil Mean age: Not reported Sex (%Male): Not reported	%Medicated: 100% Dx: Schizophrenia	Plasma	TRYP: NS
Domino et al. [138]	Total: 63 Case: 27 Control: 36	Country: United States of America Age (range): 24-46 (cases), 19-53 (controls) Sex (%Male): 100%	%Medicated:0% Dx: Schizophrenia	Plasma	TRYP: ↑
Fazio et al. [52]	Total: 174 Case: 90 Control: 84	Country: Italy Mean age: 33.1 Sex (%Male): 56%	%Medicated: >50% Dx: Schizophrenia	Serum	TRYP: NS KYN: NS KYNA: NS 3-HK: ↓ QUIN: ↓
Fekkes et al. [53]	Total: 30 Case: 13 Control: 17	Country: The Netherlands Mean age: 33.0 Sex (%Male): 48%	%Medicated: 0% Dx: Schizophrenia	Plasma	TRYP: ↓
Freedman et al. [54]	Total: 44 Case: 33 Control: 11	Country: United States of America Mean age: 31.5 Sex (%Male): 100%	%Medicated: >50% Dx: Schizophrenia	Plasma	TRYP: NS KYN: NS
Fukushima et al. [55]	Total: 52 Case: 25 Control: 27	Country: Japan Mean age: 27.4 Sex (%Male): 44%	%Medicated: 100% Dx: Schizophrenia	Serum	TRYP: ↑ KYN: ↑ KYNA: NS
Joaquim et al. [63]	Total: 58 Case: 28 Control: 30	Country: Brazil Mean age: 26.1 Sex (%Male): 57%	%Medicated: 0% Dx: Schizophrenia	Plasma	TRYP: ↓ KYN: ↓ KYN/TRYP: NS
Kim et al. [66]	Total: 245 Case: 71 Control: 174	Country: South Korea Mean age: 33.2 Sex (%Male): 45%	%Medicated: 0% Dx: Schizophrenia	Plasma	TRYP: ↓
Lee et al. [70]	Total: 214 Case Group 1: 85 Case Group 2: 74 Control: 55	Country: United States of America Mean age: 31.4 Sex (%Male): 66%	%Medicated: 0% Dx: Schizophrenia and Schizoaffective	Plasma	TRYP: ↓
Leppik et al. [71]	Total: 76 Case: 38- 36 Control: 37	Country: Estonia Mean age: 25.1 Sex (%Male): 49.7%	%Medicated: 0% Dx: Schizophrenia and First episode of psychosis	Serum	TRYP: ↓ KYN: NS KYN/TRYP: ↓
Myint et al. [88]	Total: 101 Case: 53 Control: 48	Country: South Korea Mean age: 32.9 Sex (%Male): 44%	%Medicated: 0% Dx: Schizophrenia	Plasma	KYNA ↓ 3-HK: ↑ KYNA/KYN: ↓ KYNA/3HK: ↓

Table 3 (continued)

Study name	Sample size	Study characteristics	Medical Hx	Serum / Plasma	Metabolites measured and effect direction
Oxenkrug et al. [92]	Total: 18 Case: 6 Control: 12	Country: United States of America Age (range): 38-56 Sex (%Male): 50%	%Medicated: 100% Dx: Schizophrenia	Serum	TRYP: NS KYN: NS KYNA: NS 3-HK: ↓ KYNA/KYN: NS KYN/TRYP: NS
Potkin et al. [97]	Total: 39 Case: 22 Control: 17	Country: United States of America Mean age: 30.8 Sex (%Male): Not reported	%Medicated: <50% Dx: Schizophrenia	Plasma	TRYP: NS
Rao et al. [100]	Total: 147 Case Group 1: 89 Case Group 2: 24 Control: 34	Country: Germany Mean age: 29.5 Sex (%Male): 49.5%	%Medicated: 0% (Group 1); 100% (Group2) Dx: Schizophrenia	Serum	TRYP: ↓
Rao et al. [99]	Total: 199 Case Group 1: 67 Case Group 2: 20 Case Group 3: 22 Control: 90	Country: Germany Mean age: 29.5 Sex (%Male): 53.7%	%Medicated: 0% (Group 1 and 2); 100% (Group 3) Dx: Schizophrenia	Serum	TRYP: ↓
Ravikumar et al. [101]	Total: 30 Case: 15 Control: 15	Country: India Mean age: Not reported Sex (%Male): Not reported	%Medicated: 0% Dx: Schizophrenia	Plasma	KYNA: ↑ QUIN: ↑ TRYP: ↑
Shovestul et al. [109]	Total: 20 Case: 10 Control: 10	Country: United States of America Age (range): 35-41 Sex (%Male): 50%	%Medicated: Not reported Dx: Schizophrenia and Schizoaffective	Serum	KYN: NS KYNA: NS
Sperner-Unterweger et al. [112]	Total: 20 Case: 10 Control: 10	Country: Austria Mean age: 32.3 Sex (%Male): 60%	%Medicated: >50% Dx: Schizophrenia	Serum	TRYP: NS KYN: NS
Szymona et al. [114]	Total: Case: 51 Control: 45	Country: Poland Mean age: 25.55 Sex (%Male): 57%	%Medicated: Unclear Dx: Schizophrenia	Serum	KYNA: ↓ 3-HK: NS KYNA/3HK: ↓
Tortorella et al. [116]	Total: 22 Case: 11 Control: 11	Country: Italy Mean age: 27.1 Sex (%Male): 55%	%Medicated: 0% Dx: Schizophrenia	Plasma	TRYP: ↓
van de Kerkhof et al. [118]	Total: 108 Case: 33 Control: 75	Country: The Netherlands Mean age: 35.3 Sex (%Male): 79%	%Medicated: >50% Dx: Schizophrenia	Plasma	TRYP: NS
Van der Heijden et al. [119]	Total: 139 Case: 66 Control: 73	Country: The Netherlands Mean age: 32.5 Sex (%Male): 64%	%Medicated: 0% Dx: Schizophrenia	Plasma	TRYP: NS
Wei et al. [120]	Total: 51 Case Group 1: 11 Case Group 2: 12 Control: 28	Country: United Kingdom Mean age: 39.9 Sex (%Male): 100%	%Medicated: 0% Dx: Schizophrenia	Serum	TRYP: NS
Wurfel et al. [124]	Total: 113 Case: 21 Control: 92	Country: United States of America Mean age: 35.6 Sex (%Male): 60%	%Medicated: Unclear Dx: Schizophrenia	Serum	TRYP: NS KYN: NS KYNA: NS 3-HK: NS QUIN: NS KYN/TYP: NS KYNA/3HK: NS

↑: increased in people with schizophrenia, ↓: decreased in people with schizophrenia, *NS* non-significant difference between healthy controls and people with schizophrenia, *Medical Hx* Medical History, *Dx* Diagnosis, *TRYP* Tryptophan, *KYN* Kynurenine, *KYNA* Kynurenic Acid, *3-HK* 3-Hydroxy Kynurenine, *QUIN*Quinolinic Acid, *KYNA/KYN* Kynurenic Acid/Kynurenine Ratio, *KYN/TRYP* Kynurenine/Tryptophan Ratio, *KYNA/QA* Kynurenic Acid/Quinolinic Acid Ratio, *KYNA/3HK* Kynurenic Acid/3-Hydroxy Kynurenine Ratio.

95% CI = −0.60 to 0.49, $p = 0.85$, $I^2 = 85\%$, $k = 6$, $n = 407$) (Figs. 2c and Fig. 3, and Supplementary Figs. 22–29).

A *leave-one-out* analysis significantly affected the results for kynurenic acid to kynurenine ratio, turning the results significant, with a lower ratio, when the study by Barry et al. was excluded ($g = -0.49$, 95% CI = −0.85 to −0.12, $p = 0.01$) [34]; also decreased heterogeneity was found when this study was excluded ($I^2 = 0$). This particular study had a low risk of bias but included only participants whose disorder were stable. Tryptophan was particularly susceptible to a *leave-one-out* analysis with the removal of 15 separate studies resulting in a lack of significant difference between people with SZ and controls. No other metabolite was affected by the removal of any individual study.

In a set of sub-group analyses, studies that assessed kynurenine to tryptophan ratio in plasma reported higher levels in people with SZ than healthy controls ($g = 0.36$, 95% CI = 0.004 to 0.626, $p = 0.05$) and decreased heterogeneity (I^2 = decreased from 85% to 22%), while there was no significant difference in those that measured this ratio in serum; similar results were seen for kynurenine, where kynurenine levels were decreased in plasma but not in serum (Supplementary Table 3). Meta-regression analyses on these same metabolites using mean age and sex showed no statistical significance. Due to the limited number of studies, sub-group analyses were not conducted for all metabolites (Supplementary material 2). Egger's regression test for tryptophan ($p = 0.43$) and kynurenine ($p = 0.09$) indicated no sign of publication bias (Supplementary Figs. 30 and 31). Trim-and-fill analysis did not change the original effect sizes.

Discussion

This is the largest and most comprehensive meta-analysis to investigate the role of the kynurenine pathway across major mental disorders. We report several significant differences in metabolites of the kynurenine pathway between people with MDD, BD, or SZ, and healthy controls. These differences are evident both in the main analyses, as well as in the sub-group analyses assessing metabolites in plasma, a blood source that yields more accurate results than serum [127, 128]. In particular, the results of these meta-analyses suggest that tryptophan and kynurenine are lower across all conditions studied. While kynurenic acid and the kynurenic acid to quinolinic acid ratio appear decreased in mood disorders (i.e., MDD and BD), kynurenic acid is not altered in SZ. Kynurenic acid to 3-hydroxykynurenine ratio is decreased in MDD but not in SZ. Kynurenic acid to kynurenine ratio was decreased in both MDD and SZ, and the kynurenine to tryptophan ratio was increased, again, in both MDD and SZ. However, when considering only the main analyses in SZ, only tryptophan was altered. In addition, there are no significant differences in quinolinic acid or 3-hydroxykynurenine in any included meta-analyses; this may be due to the relatively few studies included in these particular meta-analyses and also due to low sensitivity of laboratorial assays in assessing these particular metabolites. Most significant effect sizes are only small to moderate in magnitude.

Tryptophan, the main precursor of the kynurenine pathway, is decreased across all mental disorders considered. This likely reflects its relative importance in these disorders, particularly in the context of serotonin bioavailability. Decreased bioavailability of tryptophan is at least partially responsible for the depleted levels of serotonin found in MDD. This decrease in tryptophan is probably also, again, at least partially, responsible for the decreased bioavailability of kynurenine that we found across MDD, BD, and SZ. Furthermore, we also saw an increase in the kynurenine to tryptophan ratio in MDD and SZ. This suggests that the decrease in serotonin bioavailability, traditionally considered as one of the bases of the monoamine hypothesis, is secondary not only to a decreased pool of tryptophan but also to a shift in the tryptophan metabolism away from serotonin towards kynurenine in mood disorders and SZ.

While a decrease in the bioavailability of tryptophan and a shift of tryptophan metabolism from serotonin to kynurenine appears to occur in both mood disorders (MDD and BD) and in SZ, downstream kynurenine, our data suggest that biological pathways may differ. In mood disorders, kynurenic acid is lower, and the ratios of kynurenic acid to kynurenine, and of kynurenic acid to 3-hydroxykynurenine are decreased compared to healthy subjects, suggesting an imbalance between the putatively neuroprotective kynurenic acid and the neurotoxic quinolinic acid, with a preponderance of quinolinic acid. Quinolinic acid, however, is not increased in mood disorders, thus it is not possible to say if this imbalance is due to a decrease in kynurenic acid or to a decrease in kynurenic acid in tandem with an increase in quinolinic acid. Yet, in contrast to mood disorders, we found no convincing evidence of imbalance between kynurenic and quinolinic acids in SZ; both metabolites are not altered in the periphery, and the kynurenic acid to 3-hydroxykynurenine and the kynurenic acid to kynurenine ratios are also not altered.

Our results differ to some extent from prior meta-analyses [22–24]. Due to an increased number of studies included and sub-group analyzes, we were able to identify several altered metabolites and ratios. Arnone et al. [23] reported decreased kynurenine levels in MDD; however, they reported no significant difference in tryptophan, kynurenine to tryptophan ratio, the kynurenic acid to quinolinic acid ratio and no difference in any metabolite in BD.

Ogyu et al. [24], similarly to our data, reported decreased kynurenine and kynurenic acid in MDD, and also reported quinolinic acid decreased only in a sub-group analysis with only drug-free participants. Finally, consistent with our study, Plitman et al. [22] found no difference in blood kynurenic acid in SZ; however, they also reported kynurenic acid increased in the CNS.

The role of peripheral kynurenine pathway metabolites on central brain function is not fully understood. Tryptophan and kynurenine metabolites can cross the blood-brain barrier; however, the relevance of other metabolites within peripheral circulation requires further investigation. Recently, a study in people with depression reported that plasma kynurenine metabolites are correlated with kynurenine metabolites in cerebrospinal fluid and that a high plasma kynurenine to tryptophan ratio was strongly associated with depression severity [129]. Another study reported that plasma kynurenine to tryptophan ratio was inversely correlated with glutamate levels in the frontal white matter of people with SZ, suggesting that peripheral markers of kynurenine may be related to central mechanisms [40].

Similar to previously conducted meta-analyses [22–24], there was a generally high level of statistical heterogeneity in our meta-analyses; the heterogeneity in most meta-analyses decreased when we considered only plasma as the blood source. As a large number of studies included in this review did not include information regarding other potentially related factors, such as symptom severity, medication dose, smoking status, these factors were not included in our meta-analyses. We found that age and sex influenced a number of metabolites in BD but not in MDD or SZ. Furthermore, the high heterogeneity displayed in this meta-analysis suggests that kynurenine pathway metabolism is not homogenous in people with these mental disorders. To guide precision medicine efforts, the investigation of potential sub-populations that are more susceptible to alterations in the kynurenine pathway are warranted [130, 131].

Strengths and limitations

Our study analyzed several components of the kynurenine pathway across MDD, BD, and SZ; by comparing the metabolites alterations across disorders, we were able to not only identify particular alterations in metabolites, but also to derive a pattern for the kynurenine pathway in mood disorders and SZ sufficient to identify a possible divergent pattern between conditions. We also relied on a large sample size (101 studies with 10,281 subjects). Our positive results are unlikely to be substantially influenced by publication bias, given that the funnel plots were mostly symmetrical, and the trim-and-fill procedure did not point to any missing study necessary to impute in order to 'correct' the ES. In addition, through a series of sensitivity and sub-group analyses, we were able to rule out the possibility that the results were biased due to a unique outlier. This approach also allowed us to investigate and rule out any single study as the sole source of the high heterogeneity found in virtually all analyses.

Notwithstanding its strengths, our study has some limitations; we included only studies that assessed the kynurenine pathway in peripheral blood; as discussed, we do not know how well peripheral levels reflect brain levels, or activity, of these metabolites. Also, for BD, we grouped all studies together, regardless of mood state; our sub-group analyzes according to mood state suggest that alterations can be greater during acute episodes but the number of studies for each metabolite in each mood state was small and these results are exploratory. Another point is the possible role of diet in modulating tryptophan metabolites. Emerging studies suggest that dietary components can influence tryptophan and kynurenine metabolites [132–134]. The included studies did not describe diet composition of the participants; however, previous studies demonstrate that people with mental illness report dietary patterns that are different to healthy controls [135]. It is possible that the participants with a psychiatric disorder had a different diet composition compared to controls and this might have influenced the results [136]. Finally, the metabolites were assessed using a variety of laboratory techniques. Due to the high variability and inconsistent reporting of relevant methods, we did not perform sub-group analyzes according to technique.

Conclusions

This is the first meta-analysis to examine the differences in kynurenine metabolites and to ascertain the kynurenine pathway alteration across MDD, BD, and SZ. In particular, tryptophan and kynurenine are decreased across MDD, BD, and SZ; kynurenic acid and the kynurenic acid to quinolinic acid ratio are decreased in mood disorders (i.e., MDD and BD), whereas kynurenic acid is not altered in SZ; kynurenic acid to 3-hydroxykynurenine ratio is decreased in MDD but not SZ. Kynurenic acid to kynurenine ratio is decreased in both MDD and SZ, and the kynurenine to tryptophan ratio is increased, again, in both MDD and SZ. Taken together, our results suggest that there is a shift in the tryptophan metabolism from serotonin to the kynurenine pathway, across these psychiatric disorders. In addition, a differential pattern exists between mood disorders and SZ, with a preferential metabolism of kynurenine to the potentially neurotoxic quinolinic acid instead of the neuroprotective kynurenic acid in mood disorders but not in SZ. Further

studies are required to examine the individual characteristics that modulate kynurenine metabolism in these disorders and to investigate potential treatment options that target the kynurenine pathway in an individualized way as preconized by precision psychiatry [130, 131].

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Compliance with ethical standards

Conflict of interest BSF, APD, AFC, BS, JC, MS, ML, SGC, PTT, WM, AJM, TR, AR, AJW, PYL, MB, AON, FJ, and JCS have no conflict of interest regarding this manuscript. GC from APC Microbiome Ireland has conducted studies in collaboration with several companies, including GSK, Pfizer, Cremo, Suntory, Wyeth, Mead Johnson, Nutricia, 4D Pharma, and DuPont. GC has been an invited speaker at meetings organized by Janssen and is receipt of research funding from Pharmavite. GC is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this report.

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Affiliations

Wolfgang Marx[1] · Amelia J. McGuinness[1] · Tetyana Rocks[1] · Anu Ruusunen[1,2,3] · Jasmine Cleminson[1] · Adam J. Walker[1] · Susana Gomes-da-Costa[4] · Melissa Lane[1] · Marsal Sanches[5,6] · Alexandre P. Diaz[5,6] · Ping-Tao Tseng[7] · Pao-Yen Lin[8,9] · Michael Berk[1] · Gerard Clarke[10] · Adrienne O'Neil[1] · Felice Jacka[1] · Brendon Stubbs[11,12] · André F. Carvalho[13,14] · João Quevedo[5,6] · Jair C. Soares[5,6] · Brisa S. Fernandes[5,6]

[1] Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia

[2] Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

[3] Department of Psychiatry, Kuopio University Hospital, Kuopio, Finland

[4] Bipolar and Depression Disorders Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

[5] Center of Excellence on Mood Disorders, Faillace Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA

[6] Translational Psychiatry Program, Faillace Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA

[7] Institute of Biomedical Sciences and Prospect Clinic for Otorhinolaryngology & Neurology, National Sun Yat-sen University, Kaohsiung, Taiwan

[8] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

[9] Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

[10] Department of Psychiatry and Neurobehavioural Science and APC Microbiome Ireland, University College Cork, Cork, Ireland

[11] Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK

[12] South London and Maudsley NHS Foundation Trust, London, UK

[13] Department of Psychiatry, University of Toronto, Toronto, ON, Canada

[14] Centre for Addiction and Mental Health, Toronto, ON, Canada