# Plasma L-Tryptophan Concentration in Major Depressive Disorder: New Data and Meta-Analysis

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## ABSTRACT

***Objective:*** Tryptophan, an essential amino acid, is the precursor to serotonin and is metabolized mainly by the kynurenine pathway. Both serotonin and kynurenine have been implicated in the pathophysiology of major depressive disorder (MDD). However, plasma tryptophan concentration in patients with MDD has not unequivocally been reported to be decreased, which prompted us to perform a meta-analysis on previous studies and our own data.

***Data Sources:*** We searched the PubMed database for case-control studies published until August 31, 2013, using the search terms *plasma* AND *tryptophan* AND synonyms for MDD. An additional search was performed for the term *amino acid* instead of *tryptophan*. We obtained our own data in 66 patients with MDD (*DSM-IV*) and 82 controls who were recruited from March 2011 to July 2012. The majority of the patients were medicated (N = 53). Total plasma tryptophan concentrations were measured by the liquid chromatography/mass spectrometry method.

***Study Selection:*** We scrutinized 160 studies for eligibility. Original articles that were written in English and documented plasma tryptophan values in patients and controls were selected.

***Data Extraction:*** We included 24 studies from the literature and our own data in the meta-analysis, which involved a total of 744 patients and 793 controls. Data on unmedicated patients (N = 156) and their comparison subjects (N = 203) were also extracted. To see the possible correlation between tryptophan concentrations and depression severity, meta-regression analysis was performed for 10 studies with the Hamilton Depression Rating Scale 17-item version score.

***Results:*** In our case-control study, mean (SD) plasma tryptophan level was significantly decreased in the MDD patients versus the controls (53.9 [10.9] vs 57.2 [11.3] μmol/L; $P = .03$). The meta-analysis after adjusting for publication bias showed a significant decrease in patients with MDD with a modest effect size (Hedges *g*, −0.45). However, analysis on unmedicated subjects yielded a large effect (Hedges *g*, −0.84; $P = .00015$). We found a weak association with depression severity in the meta-regression analysis ($P = .049$).

***Conclusions:*** This meta-analysis provides convincing evidence for reduced plasma tryptophan levels in patients with MDD, particularly in unmedicated patients.

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Depression imposes a great burden on afflicted individuals and society, while its pathophysiology remains elusive. Since the serotonin hypothesis was proposed by Coppen,[1] it has long been a major hypothesis in the pathophysiology of major depressive disorder (MDD). Early evidence supporting the serotonin hypothesis was decreased plasma levels of tryptophan, the amino acid precursor to serotonin.[2] Subsequently, growing evidence has suggested that tryptophan may play an important role in MDD through the kynurenine pathway as well.[3–5] In the inflammation-associated depression, for example, proinflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO), the first and rate-limiting enzyme that degrades tryptophan along the kynurenine pathway, which would result in decreased plasma tryptophan. However, in recent studies, plasma tryptophan concentration in patients with MDD has not unequivocally been reported to be lower when compared with that of controls. Some studies found significantly decreased plasma tryptophan levels in MDD patients compared with healthy controls,[6–9] while others obtained contradictive negative results.[10–12] These inconsistent results require further investigations and warrant performing meta-analysis. To our knowledge, there is no study of meta-analysis on plasma tryptophan levels in MDD. In addition, most previous studies were conducted in white subjects. To our knowledge, there have been only 2 studies from Asian populations. Xu et al[9] reported reduced tryptophan levels in Han Chinese patients with MDD compared with controls, while Myint et al[10] reported no significant difference in plasma tryptophan levels between Korean patients with MDD and controls, although "tryptophan breakdown index" was found to be increased in the patients.

The aims of the present study were 2-fold: to examine whether plasma tryptophan concentration is different between Japanese patients with MDD and controls, and to perform meta-analysis on previous studies, including ours, to determine whether plasma tryptophan concentration is lowered in MDD patients.

## DATA SOURCES

### Our Case-Control Study

***Subjects.*** Subjects were 66 patients with MDD and 82 healthy controls; they were also included in this meta-analysis. Participants were recruited at the outpatient clinic of the National Center of Neurology and Psychiatry (NCNP) Hospital, Tokyo, Japan, or through advertisements in free local magazines and our website announcement. Diagnosis

**Clinical Points**

- Patients with major depressive disorder (MDD) have decreased plasma tryptophan levels compared with healthy controls.
- Decrease in plasma tryptophan levels may be more marked for unmedicated than medicated patients.
- There may be a weak correlation between severity of MDD and plasma tryptophan level.

of MDD according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition,[13] was made based on a structured interview, medical charts, and information from the psychiatrist in charge of the patients. All patients were interviewed by using either the Mini-International Neuropsychiatric Interview (M.I.N.I.)[14] (N = 54) or the Structured Clinical Interview for *DSM-IV* Axis I disorders[15] (N = 12) by a research psychiatrist. Depression severity was assessed by the Hamilton Depression Rating Scale 17-item version (HDRS-17).[16] Remitted patients (HDRS-17 score < 8) and those patients with comorbid other Axis I disorders were not enrolled. Additional exclusion criteria for study participation were as follows: having a prior medical history of central nervous system disease or severe head injury; having a history of substance abuse/dependence; taking corticosteroids, antihypertensives, or oral contraceptives; and being on hormone replacement therapy.

Of the 66 MDD patients, there were 13 patients who did not take any psychotropic drugs at the time of study. The remaining 53 patients were medicated with psychotropic drugs such as antidepressants, antipsychotics, and benzodiazepine derivatives. There were 37 patients on antidepressant medication (mean imipramine equivalent dose: 114.9 ± 76.2 mg/d), 22 on antipsychotic medication (mean chlorpromazine equivalent dose: 178.8 ± 184.1 mg/d), and 38 on benzodiazepines (mean diazepam equivalent dose: 7.4 ± 4.8 mg/d). There were 19 patients who had a history of admission to the psychiatric ward and 7 who had a history of attempted suicide.

The present study was conducted in accordance with the Declaration of Helsinki. After the nature of the study procedures had been fully explained, written informed consent was obtained from every subject. This study was approved by the ethics committee of the NCNP (No. A2010-007).

### Blood Collection and Measurement of the Plasma Tryptophan Concentration

Measurement of plasma tryptophan concentration was done in the "real world" setting. Without fasting, venous blood was drawn between 9:30 AM and 4:30 PM to an ethylenediaminetetraacetic acid disodium (EDTA-2Na)–containing Vacutainer tube (Terumo, Tokyo, Japan), immediately centrifuged at 3000 rpm for 15 min at 4°C (H-103HR, Kokusan, Tokyo, Japan), and supernatant was collected into a polyethylene tube and stored at −20°C until analysis. Plasma tryptophan concentration was measured using the liquid chromatography/mass spectrometry (LC-MS) method at SRL Co, Inc (Hachioji, Tokyo, Japan). In plasma, tryptophan takes 2 forms (ie, free and loosely albumin-bound forms). We obtained plasma total (free + albumin-bound forms) tryptophan levels.

## STUDY SELECTION

Relevant studies published in English were identified from systematic searches of the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed?otool=ijpncnplib) through all publications available up to August 31, 2013. The following search terms were used: *plasma* AND *tryptophan* AND (*depress**[title] OR *mood disorder*[title] OR *mood disorders*[title] OR *affective disorder*[title] OR *affective disorders*[title]) AND (*normal* OR *healthy* OR *comparison* OR *control* OR *controls*).

This search strategy obtained a total of 159 records. In addition, the study of Pinto et al[11] was found by using another search term *amino acid* instead of *tryptophan* to extend our search in the PubMed database. We then scrutinized eligibility of articles for meta-analysis. Studies on minor depression and seasonal affective disorder (MDD with seasonal pattern) were excluded. The study of Maes et al[6] was excluded from analysis because the participants seemed to overlap in another study of Maes and Rief[7] The study selection flow is shown in Figure 1 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org), which outlines the preferred way to report meta-analysis studies.[17]

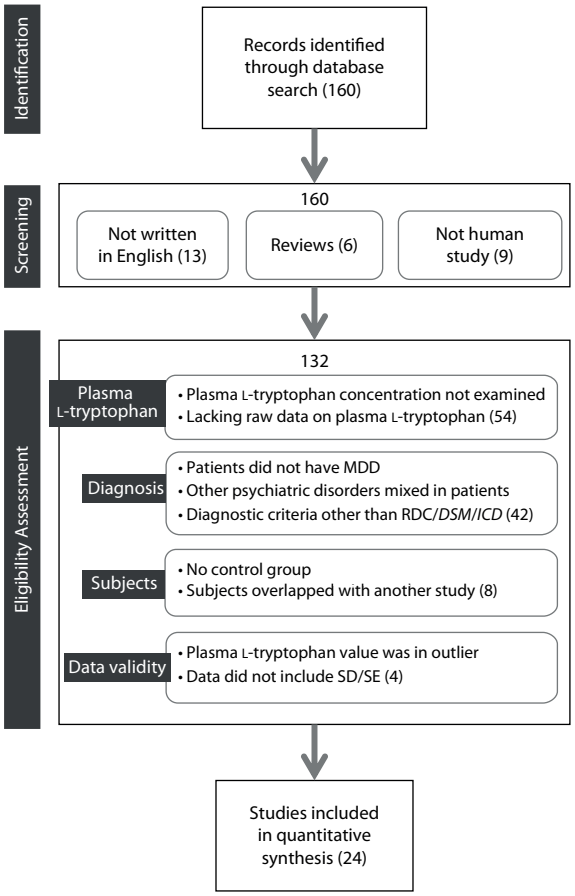
Finally, 24 articles were selected. Study quality of each article was assessed using the checklist of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (http://www.strobe-statement.org), which describes the preferred way to report observational studies.[18] Following a previous report,[19] studies were assigned a low, medium, or high possibility of reporting bias depending on how many items were checked (cutoff points were set at 33% and 66%). No study was classified as having high possibility of reporting bias. We included our case-control data in the meta-analysis.

## DATA EXTRACTION

### Our Case-Control Study

For our subjects, averages are reported as mean (SD). Ratios of categorical variables and means of continuous variables with normal distribution were compared using $\chi^2$ test and *t* test, respectively. Analysis of covariance (ANCOVA) was performed to examine the effect of diagnosis on plasma tryptophan levels controlling for age, sex, and body mass index (BMI). The possible association between HDRS-17 score and tryptophan level was examined by multiple regression analysis within the patient group, controlling for age, sex, and BMI. Statistical significance was set at 2-tailed $P < .05$. Analyses were performed using the Statistical Package for Social Science (SPSS) Japanese edition version 11.0 (SPSS Japan, Tokyo).

**Figure 1. Flowchart of the Literature Search and Eligibility Assessment**




Abbreviations: *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*, *ICD* = *International Classification of Diseases*, MDD = major depressive disorder, RDC = Research Diagnostic Criteria.

### Meta-Analytic Method

Data on means and SDs for plasma tryptophan concentration in MDD patients and controls were drawn from each study. We used the Comprehensive Meta-Analysis software (version 2.2.04; Biostat, Englewood, New Jersey). Tryptophan concentration data expressed as a unit of measure other than μmol/L (eg, μg/mL) were converted to data using the μmol/L unit. We chose Hedges *g*[20] for expressing the effect size of meta-analysis. To evaluate the effect size, we used the method of interpretation from Cohen convention.[21–23] Four studies[24–27] reported means and SDs of plasma tryptophan concentration only for subgroups (ie, MDD with and without melancholia; young and elderly groups). In these studies, we recalculated means and SDs for the total MDD patients.

Furthermore, we extracted data on unmedicated patients and their comparison subjects from 8 studies and from our own data and performed meta-analysis similarly.

Meta-regression analysis was also performed on the Comprehensive Meta-Analysis software. We chose only studies that used the HDRS-17 for estimating severity because this scale was most commonly used in the 24 studies.

**Table 1. Demographic and Clinical Data of Our Case-Control Study[a]**

| Variable[b] | Patients With MDD | Healthy Controls | Differences |
|---|---|---|---|
| Patients, N (n female/n male) | 66 (31/35) | 82 (54/28) | $\chi^2_1 = 5.3$, $P = \mathbf{.021}$ |
| Age (y) | 44.0 ± 12.9 | 43.9 ± 13.9 | $t_{146} = -0.06$, $P = .95$ |
| BMI | 22.9 ± 4.8 | 22.1 ± 3.5 | $t_{146} = -1.19$, $P = .24$ |
| HDRS-17 score | 14.3 ± 5.0 | NA | NA |
| Tryptophan (μmol/L) | 53.9 ± 10.9 | 57.2 ± 11.3 | $F_1 = 4.83$, $P = \mathbf{.030}$[a] |

[a]Based on analysis of covariance (ANCOVA) controlling for age, sex, and BMI. Significant *P* values are denoted in bold text.
[b]Variables shown as mean (SD) except for N/n values included in the first row.
Abbreviations: BMI = body mass index, HDRS-17 = Hamilton Depression Rating Scale 17-item version, MDD = major depressive disorder, NA = not applicable.

Studies that were unclear as to which version (HDRS-17 or -21) was used were excluded.

## RESULTS

### Our Case-Control Study

Demographic and clinical data, including plasma tryptophan levels, are shown in Table 1. There was no significant difference in mean age or BMI between the patients with MDD and controls; however, there was a significant difference in sex distribution ($P = .021$). ANCOVA analysis controlling for age, sex, and BMI showed a significant main effect of diagnosis ($F_1 = 4.83$, $P = .030$) on tryptophan concentration, indicating that plasma tryptophan concentration was lower in the patients than in the controls (53.9 [10.9] vs 57.2 [11.3] μmol/L). In multiple regression analysis within the patient group, there was no evidence for an association between HDRS score and tryptophan levels ($t_{4,61} = -0.24$, $P = .81$).

### Meta-Analysis

Details of the 24 articles selected for meta-analysis[7–12,24–41] are described in Table 2. Data from the 24 articles and our study yielded 25 comparisons (Figure 2A). The total numbers of patients with MDD and controls were 744 and 793, respectively. Since we detected significant heterogeneity across the studies ($P < .001$), we employed the random effects model. In the combined sample, there was a highly significant difference in standardized mean tryptophan concentration between patients and controls (Hedges *g*, −0.63; 95% CI, −0.82 to −0.44; $P < .00000001$; fail-safe number, 687). Funnel plot and Egger's regression analysis indicated a publication bias (intercept, −2.19; 95% CI, −3.81 to −0.58; $df = 23$; $P = .0098$). We then used "trim-and-fill method"[42] to adjust for the bias (Figure 2B). After the adjustment, the Hedges *g* showed a modest effect (Hedges *g*, −0.45; 95% CI, −0.66 to −0.23), although the statistical significance remained high ($P = .00006$) (Figure 2B).

We also performed meta-analysis in patients who did not take psychotropic drugs, which yielded 9 comparisons. The total numbers of patients with MDD and controls were 156

**Table 2. Characteristics of Studies Included in Meta-Analysis on Comparison With Plasma L-Tryptophan Concentration Between Patients With MDD and Healthy Controls**

| Study | Subjects' Country (race) | Case Group Name (criteria) | Case N (n female/ n male) | Mean (SD) Plasma L-Tryptophan Concentration (μmol/L) | Control N (n female/ n male) | Mean (SD) Plasma L-Tryptophan Concentration (μmol/L) | Evaluation of Depressive State (mean [SD] score) | Drug Free in Patients[a] (period) |
|---|---|---|---|---|---|---|---|---|
| DeMyer et al, 1981[41] | USA | MDD (RDC) | 18 (13/5) | 42 (11) | 10 (7/3) | 56.9 (12) | HDRS-17 (22.4 [8.9]) | Yes (3 wk) |
| Menna-Perper et al, 1983[40] | USA | MDD with melancholia (*DSM-III*) | 9 (3/6) | 42.8 (8.2) | 6 (3/3) | 46.3 (4.7) | HDRS, BDI (NA) | No |
| Joseph et al, 1984[39] | USA | MDD (*DSM-III*) | 16 (10/6) | 31.3 (7.2) | 8 (5/3) | 43.8 (16) | HDRS, BDI (NA) | Yes (1 wk) |
| Anderson et al, 1990[38] | UK | MDD (*DSM-III*) | 31 (15/16) | 38.2 (8.9) | 31 (15/16) | 45.4 (11.1) | HDRS-17 (22.8 [NA]) | No |
| Chiaroni et al, 1990[37] | France, Switzerland | MRD (*DSM-III*) | 25 (19/6) | 48.8 (13.3) | 33 (19/14) | 59.5 (12.7) | AMDP (NA) | No |
| Russ et al, 1990[36] | USA | MDD (*DSM-III-R*) | 16 (10/6) | 59 (11) | 9 (7/2) | 52 (14) | HDRS-21 (31 [7]) | No |
| Maes et al, 1990[24] | Belgium | MDD – melancholia (*DSM-III*) | 22 (12/10) | 56.6 (10.5) | 16 (8/8) | 60.6 (4.8) | HDRS (NA) | No |
| | | MDD + melancholia (*DSM-III*) | 13 (7/6) | 50 (12.1) | 16 (8/8) | 60.6 (4.8) | HDRS (NA) | |
| Price et al, 1991[35] | USA | MDD (*DSM-III-R*) | 109 (78/31) | 35.3 (8.3) | 58 (41/17) | 36.7 (8.3) | HDRS-25 (34 [11]) | No |
| Quintana, 1992[33] | Spain | MDD (RDC) | 25 (15/10) | 42.5 (8.3) | 25 (NA) | 47.6 (11.3) | HDRS (NA) | No |
| Lucca et al, 1992[34] | Italy | MDD (*DSM-III-R*) | 19 (12/7) | 52 (20) | 29 (14/15) | 74 (12) | HDRS-21 (24.7 [4.1]) | No |
| Maes et al, 1993[25] | Belgium | MDD – melancholia (*DSM-III-R*) | 7 (NA) | 56 (14) | 8 (NA) | 79 (12) | HDRS (NA) | No |
| | | MDD + melancholia (*DSM-III-R*) | 10 (NA) | 55 (15) | 8 (NA) | 79 (12) | HDRS (NA) | |
| Ortiz et al, 1993[26] | Spain | MDD adults (*DSM-III-R*) | 10 (8/2) | 69.0 (9.8) | 10 (NA) | 70.0 (14.7) | MADRS (26.8 [2.0]) | No |
| | | MDD elderly (*DSM-III-R*) | 7 (5/2) | 64.1 (8.8) | 10 (NA) | 70.0 (14.7) | MADRS (28.3 [1.4]) | |
| Moller, 1993[32] | Denmark | All depressives (*DSM-III*) | 26 (18/8) | 36 (6) | 55 (39/16) | 39 (8) | HDRS-17 (24 [5]) | No |
| Maes et al, 1995[27] | Belgium | MDD – melancholia (*DSM-III*) | 47 (35/12) | 61 (12) | 50 (24/26) | 66 (12) | HDRS-17 (21.3 [2.9]) | No |
| | | MDD + melancholia (*DSM-III*) | 35 (21/14) | 57 (12) | 50 (24/26) | 66 (12) | HDRS-17 (26.7 [3.2]) | |
| Mauri et al, 1998[31] | Italy | MDD (*DSM-IV*) | 29 (14/15) | 33.3 (27.3) | 28 (12/16) | 56.7 (79.9) | HDRS (NA) | Yes (4 wk) |
| Song et al, 1998[30] | Belgium | MDD (*DSM-IV*) | 6 (4/2) | 69 (11) | 14 (6/8) | 73 (19) | (NA) | Yes (10 d) |
| Hoekstra et al, 2001[29] | Netherlands | MDD (*DSM-IV*) | 20 (13/7) | 35.5 (9) | 29 (13/16) | 45.6 (6.1) | HDRS-17 (31 [NA]) | No |
| Mauri et al, 2001[28] | Italy | MDD (*DSM-IV*) | 16 (11/5) | 28.6 (34.1) | 11 (2/9) | 45.6 (13.0) | HDRS-17 (22.4 [5.6]) | No |
| Myint et al, 2007[10] | Korea | MDD (*DSM-IV*) | 58 (32/26) | 65.8 (15.6) | 189 (86/103) | 69.7 (13.7) | HDRS-17 (27.2 [7.3]) | No |
| Manjarrez-Gutierrez et al, 2009[8] | Mexico | MDD (*DSM-IV*) | 8 (4/4) | 48.1 (1.2) | 9 (5/4) | 57.7 (3.3) | (NA) | Yes (NA) |
| Sublette et al, 2011[12] | USA (white/ nonwhite) | MDD (*DSM-IV*) | 30 (14/16) | 59.2 (10.4) | 31 (21/10) | 60.2 (7.7) | HDRS-17 (20.1 [3.4]) BDI (25.9 [8.2]) | No |
| Maes and Rief, 2012[7] | Germany | MDD (*DSM-IV*) | 35 (22/13) | 69.8 (14.4) | 22 (8/14) | 82.9 (15.9) | BDI (27.1 [8.3]) | Yes (NA) |
| Pinto et al, 2012[11] | Brazil | MDD (*DSM-IV*) | 5 (NA) | 35 (6) | 5 (NA) | 36 (2) | HDRS (22 [2]) | Yes (NA) |
| Xu et al, 2012[9] | China (Han Chinese) | MDD (*DSM-IV*) | 26 (19/7) | 42.9 (6.4) | 25 (16/9) | 49.8 (7.2) | HDRS-17 (24.2 [4.5]) | Yes (NA) |

[a]*Drug free* means being completely excepted from the administration of psychotropic drugs, not only antidepressants but also benzodiazepines and antipsychotics.

Abbreviations: AMDP = The Association for Methodology and Documentation in Psychiatry, BDI = Beck Depression Inventory, *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MRD = major recurrent depression, NA = not mentioned in the article, RDC = Research Diagnostic Criteria, TRP = plasma L-tryptophan.

and 203, respectively (Figure 2C). There was a significant heterogeneity ($P = .002$), and the random effects model was applied. As a result, there was a highly significant difference in standardized mean tryptophan concentration between the 2 groups (Hedges *g*, −0.84; 95% CI, −1.27 to −0.40; $P = .00015$; fail-safe number, 93). Funnel plot and Egger regression analysis did not indicate publication bias (intercept, −2.73; 95% CI, −6.92 to 1.47; $df = 7$; $P = .17$) (Figure 2D).

To elucidate the relationship between plasma tryptophan concentration and depression severity, we performed meta-regression analysis in 11 comparisons (Figure 3A). When we set the HDRS-17 score as an outcome variable and Hedges *g* value as an explanatory variable, we found that Hedges *g* value had a significant, albeit weak, effect on HDRS-17 score by adopting the fixed effects model as the estimation method ($\tau^2 = 0.068$, slope, −0.029; 95% CI, −0.057 to −0.00012; $P = .049$) (Figure 3B).

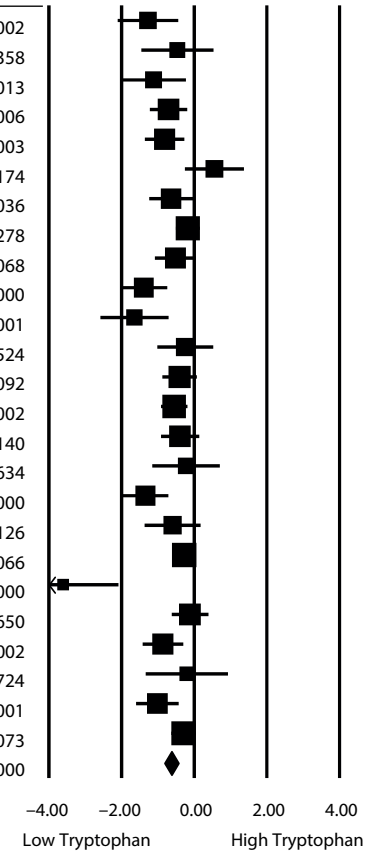
## DISCUSSION

In our case-control study, the ANCOVA analysis controlling for age, sex, and BMI showed that the patients with MDD had significantly lower plasma tryptophan

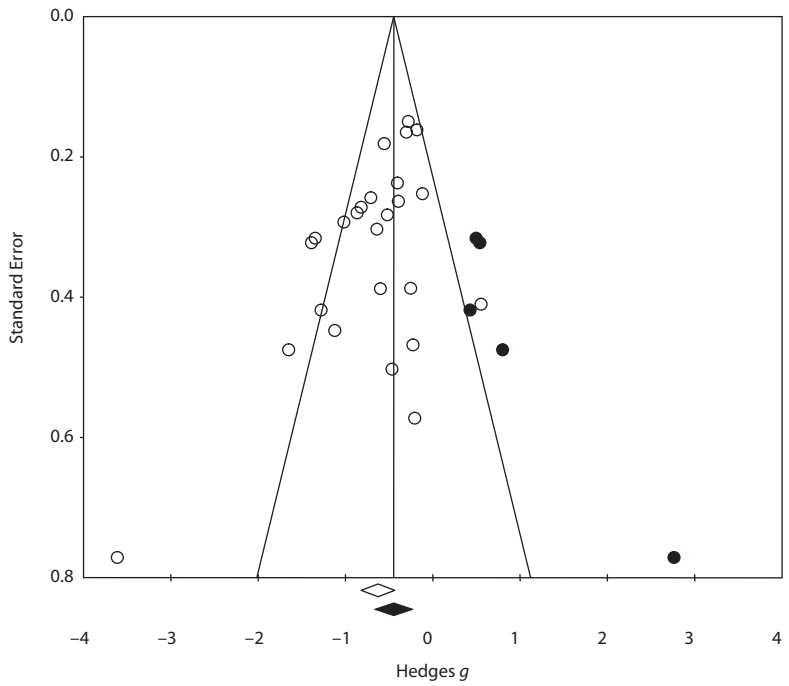
**Figure 2. Forest Plots and Funnel Plots of Meta-Analysis[a]**

A. Forest Plot of Meta-Analysis on 25 Comparisons

| Study | Hedges *g* | Standard Error | Lower Limit | Upper Limit | *Z* Value | *P* Value |
|---|---|---|---|---|---|---|
| DeMyer et al, 1981[41] | −1.274 | 0.419 | −2.095 | −0.453 | −3.040 | .002 |
| Menna-Perper et al, 1981[40] | −0.462 | 0.503 | −1.449 | 0.524 | −0.919 | .358 |
| Joseph et al, 1984[39] | −1.117 | 0.448 | −1.995 | −0.239 | −2.492 | .013 |
| Anderson et al, 1990[38] | −0.705 | 0.259 | −1.212 | −0.198 | −2.726 | .006 |
| Chiaroni et al, 1990[37] | −0.815 | 0.272 | −1.348 | −0.281 | −2.992 | .003 |
| Russ et al, 1990[36] | 0.558 | 0.411 | −0.247 | 1.363 | 1.359 | .174 |
| Maes et al, 1990[24] | −0.635 | 0.304 | −1.231 | −0.040 | −2.092 | .036 |
| Price et al, 1991[35] | −0.176 | 0.162 | −0.493 | 0.142 | −1.084 | .278 |
| Quintana, 1992[33] | −0.516 | 0.283 | −1.071 | 0.039 | −1.822 | .068 |
| Lucca et al, 1992[34] | −1.385 | 0.323 | −2.018 | −0.752 | −4.289 | .000 |
| Maes et al, 1993[25] | −1.645 | 0.475 | −2.577 | −0.713 | −3.461 | .001 |
| Ortiz et al, 1993[26] | −0.247 | 0.388 | −1.008 | 0.513 | −0.637 | .524 |
| Moller, 1993[32] | −0.400 | 0.238 | −0.866 | 0.066 | −1.683 | .092 |
| Maes et al, 1995[27] | −0.551 | 0.182 | −0.907 | −0.195 | −3.035 | .002 |
| Mauri et al, 1998[31] | −0.389 | 0.264 | −0.906 | 0.128 | −1.475 | .140 |
| Song et al, 1998[30] | −0.223 | 0.469 | −1.142 | 0.695 | −0.476 | .634 |
| Hoekstra et al, 2001[29] | −1.341 | 0.316 | −1.961 | −0.721 | −4.238 | .000 |
| Mauri et al, 2001[28] | −0.595 | 0.388 | −1.356 | 0.166 | −1.532 | .126 |
| Myint et al, 2007[10] | −0.276 | 0.150 | −0.570 | 0.018 | −1.838 | .066 |
| Manjarrez-Gutierrez et al, 2009[8] | −3.607 | 0.772 | −5.120 | −2.095 | −4.675 | .000 |
| Sublette et al, 2011[12] | −0.115 | 0.253 | −0.611 | 0.381 | −0.453 | .650 |
| Maes and Rief, 2012[7] | −0.862 | 0.280 | −1.411 | −0.313 | −3.076 | .002 |
| Pinto et al, 2012[11] | −0.202 | 0.573 | −1.325 | 0.921 | −0.352 | .724 |
| Xu et al, 2012[9] | −1.014 | 0.293 | −1.589 | −0.438 | −3.454 | .001 |
| Present Study | −0.297 | 0.165 | −0.621 | 0.027 | −1.795 | .073 |
| Total | −0.627 | 0.098 | −0.819 | −0.436 | −6.407 | .000 |




B. Funnel Plot of Standard Error by Hedges *g*

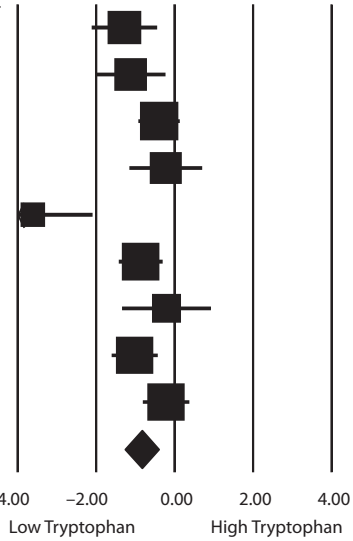



*(continued)*

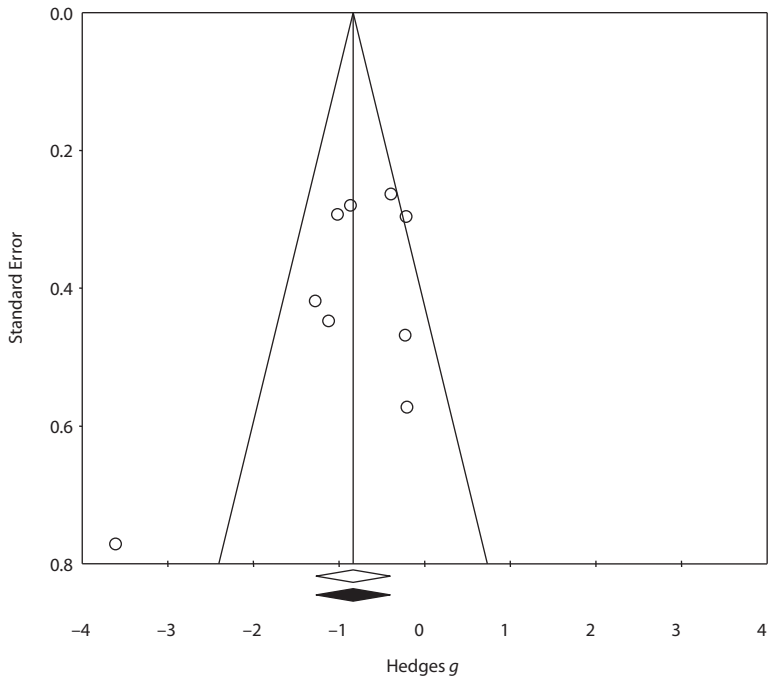
**Figure 2 (continued). Forest Plots and Funnel Plots of Meta-Analysis[a]**

C. Forest Plot of Meta-Analysis Using Psychotropic Drug–Free Patients of Our Subjects and Previous Studies

| Study | Hedges *g* | Standard Error | Lower Limit | Upper Limit | *Z* Value | *P* Value |
|---|---|---|---|---|---|---|
| DeMyer et al, 1981[41] | −1.274 | 0.419 | −2.095 | −0.453 | −3.040 | .002 |
| Joseph et al, 1984[39] | −1.117 | 0.448 | −1.995 | −0.239 | −2.492 | .013 |
| Mauri et al, 1998[31] | −0.389 | 0.264 | −0.906 | 0.128 | −1.475 | .140 |
| Song et al, 1998[30] | −0.223 | 0.469 | −1.142 | 0.695 | −0.476 | .634 |
| Manjarrez-Gutierrez et al, 2009[8] | −3.607 | 0.772 | −5.120 | −2.095 | −4.675 | .000 |
| Maes and Rief, 2012[7] | −0.862 | 0.280 | −1.411 | −0.313 | −3.076 | .002 |
| Pinto et al, 2012[11] | −0.202 | 0.573 | −1.325 | 0.921 | −0.352 | .724 |
| Xu et al, 2012[9] | −1.014 | 0.293 | −1.589 | −0.438 | −3.454 | .001 |
| Present Study | −0.213 | 0.297 | −0.794 | 0.368 | −0.718 | .473 |
| Total | −0.836 | 0.220 | −1.268 | −0.404 | −3.790 | .000 |




D. Funnel Plot of Standard Error by Hedges *g*

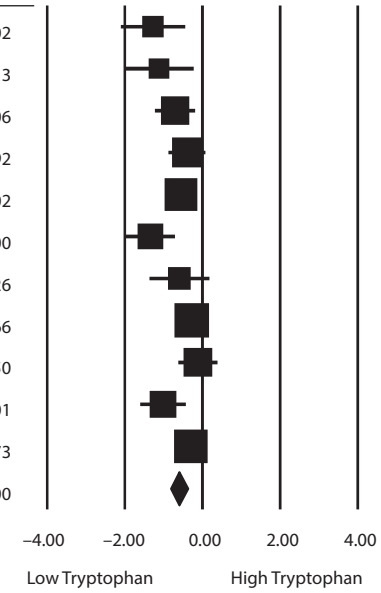



[a]The forest plots describe statistical data and effect size of each study, and the result of quantitative synthesis. Black squares depict effect size, and horizontal bars indicate 95% confidence interval. The funnel plots, which were made to examine the presence of publication bias, depict the effect size against the standard error of individual studies. Black circles represent potentially missing trials that were imputed based on the trim-and-fill method. The white rhombus represents the point estimate for plasma tryptophan concentration effect based on published trials. The black rhombus represents the new point estimate for the effect size of plasma tryptophan when publication bias was adjusted by means of the trim-and-fill method.

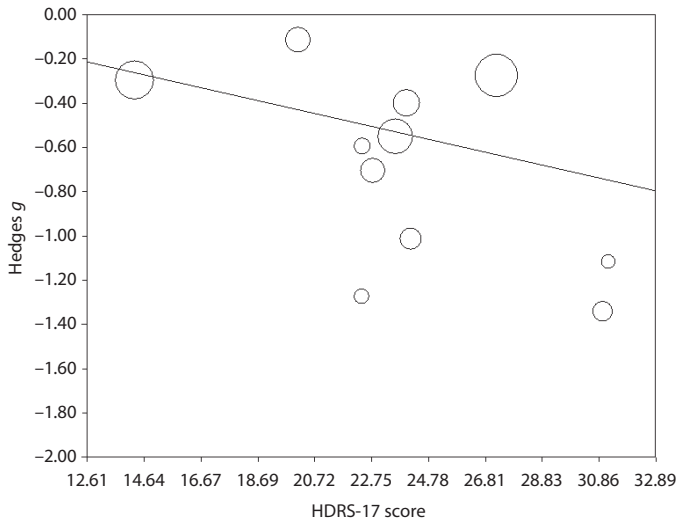
**Figure 3. Forest Plot and Scatter Plot of Meta-Regression on HDRS-17 Scores and Effect Size (Hedges *g*)[a]**

A.

| Study | Hedges *g* | Standard Error | Lower Limit | Upper Limit | *Z* Value | *P* Value |
|---|---|---|---|---|---|---|
| DeMyer et al, 1981[41] | −1.274 | 0.419 | −2.095 | −0.453 | −3.040 | .002 |
| Joseph et al, 1984[39] | −1.117 | 0.448 | −1.995 | −0.239 | −2.492 | .013 |
| Anderson et al, 1990[38] | −0.705 | 0.259 | −1.212 | −0.198 | −2.726 | .006 |
| Moller, 1993[32] | −0.400 | 0.238 | −0.866 | 0.066 | −1.683 | .092 |
| Maes et al, 1995[27] * | −0.551 | 0.182 | −0.907 | −0.195 | −3.035 | .002 |
| Hoekstra et al, 2001[29] | −1.341 | 0.316 | −1.961 | −0.721 | −4.238 | .000 |
| Mauri et al, 2001[28] | −0.595 | 0.388 | −1.356 | 0.166 | −1.532 | .126 |
| Myint et al, 2007[10] | −0.276 | 0.150 | −0.570 | 0.018 | −1.838 | .066 |
| Sublette et al, 2011[12] * | −0.115 | 0.253 | −0.611 | 0.381 | −0.453 | .650 |
| Xu et al, 2012[9] | −1.014 | 0.293 | −1.589 | −0.438 | −3.454 | .001 |
| Present Study | −0.297 | 0.165 | −0.621 | 0.027 | −1.795 | .073 |
| Total | −0.603 | 0.114 | −0.827 | −0.379 | −5.277 | .000 |




B.




[a]The forest plot of 11 comparisons for meta-regression shows statistical data and effect size on each trial and result of quantitative synthesis (A). Scatter plot and regression line depict the result of meta-regression analysis. Those circles represent each trial (B). Our selected method for estimating was "method of moments," which is a mixed-effects model rather than fixed-effect model, for carrying out this meta-regression.
*As described in the Meta-Analytic Method section, values of subgroups of patients (n, SD, mean) were united into one group.
Abbreviation: HDRS-17 = Hamilton Depression Rating Scale 17-item version.

concentrations than controls, suggesting that MDD is associated with low plasma concentration in our Japanese sample, which is in accordance with the results of the meta-analysis.

The initial meta-analysis on the total subjects indicated a heterogeneity and a publication bias. The heterogeneity may have resulted from differences in demographic and clinical characteristics, including medication across the studies. After adjustment of the publication bias, the effect size became somewhat lower (Hedges *g* of −0.45).

When the meta-analysis was performed only for patients without psychotropic medication, the obtained effect size (Hedges *g* of −0.84, ie, a large effect size) became substantially higher than that in the total subjects, suggesting that the observed difference in tryptophan concentration between patients and controls is not attributable to medication.

Rather, medication may have reduced the difference between patients and controls.

With regard to the possible correlation between depression severity and plasma tryptophan levels, we obtained no evidence for such a correlation in our Japanese sample. In the meta-regression analysis, however, we found a small but significant correlation between severity and plasma tryptophan. The failure to detect the correlation in our sample might be due in part to the small effect and that the majority of our subjects were medicated.

There might be several mechanisms underlying the association between MDD and decreased plasma tryptophan levels. Recent studies have suggested the stress- and inflammation-related mechanisms. There are enzymes to degrade tryptophan to kynurenine: tryptophan 2,3-dioxygenase (TDO) and IDO. TDO is highly expressed in the liver and activated by glucocorticoids (ie, cortisol in humans).[43,44] In line, both patients and control subjects who were administered dexamethasone, a synthetic glucocorticoid, showed lower plasma tryptophan concentrations.[24] Many studies, including ours, demonstrated that patients with MDD show hypercortisolism.[45,46] Therefore, increased enzymatic activity of TDO due to hypercortisolism is a mechanism underlying the observed reduction in plasma tryptophan levels in patients with MDD.

IDO may also play a role, since proinflammatory cytokines induce IDO activation,[47,48] and cytokine levels are elevated in MDD patients.[49] In line, a drastic fall of plasma tryptophan was observed in patients with inflammatory disorder and in those patients receiving immunotherapy.[3] Indeed, the immune system activation by hepatitis C virus infection or chronic interferon-α administration increases prevalence of MDD.[50,51] Moreover, we found higher interleukin-6 levels in cerebrospinal fluid (CSF) of MDD patients compared with controls,[52] suggesting neuroinflammation in at least a portion of the patients. In the brain, IDO is expressed in astrocytes and microglial cells. In astrocytes, kynurenine is converted to kynurenic acid, which has a neuroprotective effect by antagonizing glycine coagonist site of *N*-methyl-D-aspartate (NMDA) receptor.[53] In microglial cells, by contrast, kynurenine is predominantly converted to quinolinic acid or 3-hydroxykynurenine, which have a neurotoxic effect through agonizing the NMDA receptor.[53] Therefore, inflammation-induced activation of IDO and microglial cells might be another mechanism.

Since tryptophan is an essential amino acid, it is also possible that the dietary intake of tryptophan might be decreased in patients with MDD. The tryptophan depletion procedure is known to precipitate low mood and other symptoms of depression in vulnerable subjects and there is some evidence that tryptophan loading is effective as a treatment for depression (reviewed by Parker and Brotchie[54]). However, there is little information on the dietary tryptophan intake in depressed patients. In a population-based prospective study of 29,133 men in Finland whose intake of amino acids was calculated from a diet history questionnaire, there was no significant association between reduced dietary intake of tryptophan and depressed mood.[55] However, a possibility remains that tryptophan intake may be specifically important for depressive symptoms in persons with a diagnosed depressive disorder, as opposed to depressive symptoms within a general population. Further studies are warranted to see whether the dietary intake contributes to the observed decrease in plasma tryptophan levels in MDD.

There are several limitations in the study. We measured only total tryptophan level, so we could not address whether free tryptophan levels were different between the MDD patients and controls. In our case-control study, the measurement of plasma tryptophan level was done in the "real world" setting, ie, we did not control for fasting, time of sampling, or medication. The majority of previous studies controlled fed status (ie, overnight fasting). With respect to timing of sampling, there was no significant difference in the timing of measurement between the 2 groups (data not shown). The majority of our subjects were medicated. Benzodiazepines increase free tryptophan concentration in rat serum,[56] although conflicting negative results have also been reported in humans.[57] Antidepressants such as citalopram decrease TDO activity,[58] which may have increased plasma tryptophan level in medicated MDD patients. Therefore, medication is likely to have minimized rather than exaggerated the difference in plasma tryptophan level between our patients and controls. This is consistent with the results of our meta-analysis. Our cross-sectional study precludes us from elucidating the cause-effect relationship between low plasma tryptophan and the development of MDD. In addition, plasma tryptophan concentration may not be an index for brain tryptophan level.[59] To examine brain tryptophan levels, analyses of CSF tryptophan levels in MDD patients are currently underway. In the meta-analysis, we did not search for the literature outside of the PubMed database, which may have caused us to miss some studies included in other databases.

In conclusion, in spite of these limitations, the present study clearly indicated that MDD is associated with lower plasma tryptophan levels. Although the majority of previous studies were from Western populations, results of our case-control study are in accordance with those of Western studies regardless of differential lifestyle and dietary habits. If there is any correlation between plasma tryptophan level and depression severity, the effect size would be small.

***Drug names:*** citalopram (Celexa and others), diazepam (Diastat, Valium, and others), imipramine (Tofranil and others).

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