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Original citation & hyperlink:
Moradi, F, Lotfi, K, Armin, M, Clark, CCT, Askari, G & Rouhani, MH 2021, 'The association between serum homocysteine and depression: a systematic review and meta-analysis of observational studies', European Journal of Clinical Investigation, vol. 51, no. 5, e13486, pp. (In-press).
https://dx.doi.org/10.1111/eci.13486

DOI 10.1111/eci.13486
ISSN 0014-2972
ESSN 1365-2362

Publisher: Wiley

Title Page

The association between serum homocysteine and depression: a systematic review and meta-analysis of observational studies

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Running title: Homocysteine and depression

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/eci.13486

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Acknowledgment: M.H.R and F.M designed the study and searched databases and performed data analysis. F.M and M.A screened studies and extracted data. M.H.R and F.M and K.L and C.C contributed to the writing and revising of the manuscript. This paper was supported by the School of Nutrition and Food Science, Isfahan University of Medical Sciences.

Abstract:

Background: Hyperhomocysteinemia is known to interfere with neurological functions; however, there is a controversy regarding the relationship between homocysteine and depression.

Methods: Science Direct, MEDLINE, and ISI Web of Science were searched to find relevant articles, published up to August 2020. Studies were included if they compared homocysteine levels in healthy subjects with subjects with depression. Also, articles that reported the association between hyperhomocysteinemia and risk of depression were included. Odds ratios of depression and means of homocysteine were used to ascertain the overall effect size.

Results: Homocysteine level was higher in subjects with depression in comparison with healthy controls (weight mean difference =2.53 μmol/L, 95% confidence interval: 1.77, 3.30), and the depression diagnostic tool was a source of heterogeneity. Homocysteine level was significantly higher in subjects with depression in studies that used Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), Geriatric Depression Scale (GDS), Zung Self-Rating Depression Scale (ZDRS), and Beck Depression Index II (BDI-II) as depression diagnostic tools. Also, participants with hyperhomocysteinemia had a higher chance of depression (Pooled risk =1.34, 95% confidence interval: 1.19, 1.52), where the depression diagnostic tool was a source of heterogeneity. In contrast to ZDRS and Patient Health Questionnaire (PHQ) subgroups, hyperhomocysteinemia yielded a significantly higher risk of depression in DSM-IV, GDS, and "other" subgroups.

Conclusion: Homocysteinemia level is higher in individuals with depression. However, the depression diagnostic tool used is instrumental in influencing their association, and thus, future studies should focus on the tools for depression assessment.

Keywords: Depression, Homocysteine, Hyperhomocysteinemia, Systematic Review, Meta-analysis

Abbreviation	Definition
WMD	Weight Mean Difference
CI	Confidence Interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV

GDS	Geriatric Depression Scale
ZDRS	Zung Self-Rating Depression Scale
BDI-II	Beck Depression Index II
PHQ	Patient Health Questionnaire
ICD-10	International Statistical Classification of Disease
CESD	Center for Epidemiological Studies-Depression
SAM	S-adenosylmethionine
SAH	S-adenosylhomocysteine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Introduction:

Depression is a major cause of disability characterized by sadness, low self-worth, poor concentration, feelings of tiredness, and disturbed sleep or appetite (1), and has adverse effects on health quality of life(2). Approximately 300 million people (about 4.4% of the whole world's population) are diagnosable as being depressed (1), and is more prevalent in females and older adults, respectively (1). Many risk factors may lead to depressive disorders, such as gender, age, co-occurrence with other mental disorders, cardiovascular disease, and increased chemical compounds that perturb neurotransmitters (3-5).

Homocysteine is an α-amino acid derived from heating methionine with sulphuric acid (6), and the chemical structure of homocysteine is similar to cysteine (7). Elevated plasma homocysteine, also known as hyperhomocysteinemia, may be a risk factor for cardiovascular diseases, Parkinson's disease, and cognitive impairment (8-11). It is also associated with neurodegenerative and psychiatric disorders, such as Alzheimer's disease, schizophrenia, and anxiety (12, 13). Hyperhomocysteinemia can be caused by impaired renal function, smoking, lack of physical activity, high blood pressure, and hyperlipidemia since some lipid-lowering drugs might also have an effect on homocysteine levels(6, 12, 14); whilst excessive alcohol intake, high coffee intake and vitamin B12 and folate deficiency may increase the risk of hyperhomocysteinemia (6). Accordingly, supplementation with either folic acid or vitamin B12 has been proposed for the treatment of hyperhomocysteinemia (15).

Hyperhomocysteinemia can interfere with neurological functions in various ways (10); indeed, excitotoxicity, DNA damage, oxidative stress and inflammation caused by hyperhomocysteinemia may lead to abnormal neurological functions (10). Hyperhomocysteinemia may occur in more than 50% of patients with depression (16). Also, it is suggested that hyperhomocysteinemia can increase the risk of depression (17). However, despite evidence highlighting the putative role of hyperhomocysteinemia in depression, some studies observed no association between homocysteine levels and clinical parameters in depressive and cognitive disorders (6, 13, 18). Thus, given the equivocality regarding the association between homocysteine and depression, this systematic review and meta-analysis of observational studies sought to evaluate the association between homocysteine levels and depressive disorders.

Methods:

Search strategy:

The present systematic review meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We conducted an unrestricted systematic search

using Science Direct (www.sciencedirect.com/science/journals), MEDLINE (www.pubmed.com), and ISI Web of Science (isiwebofknowledge.com) electronic databases to identify relevant articles published up to August 2020. The following MeSH terms and keywords were searched in the title, abstract or keywords: ("depression" or "depressive disorder" or "depressive" or "depressed") and ("Homocysteine" or "Homocysteine" or "Hyperhomocysteinemia" or "tHomocysteine" or "HHomocysteine" or "adenosylhomocysteine").

Study selection:

Two independent researchers (F.M and M.A) screened the title and abstract of all identified studies and excluded unrelated and duplicate articles. Then, the full text of relevant papers was checked by F.M and M.H.R. All human observational studies that reported homocysteine levels in healthy and individuals with depression, as well as the association of homocysteine levels with the risk of depression, were included. Exclusion criteria were: *1)* animal or in vitro studies, *2)* studies in subjects aged <18 years.

Data extraction and quality assessment:

The final, recorded, data included; first author's last name, year of publication, country of study, gender-specific number of participants, sample size, mean age, study design, study duration, comorbidity, methods used to measure homocysteine, depression diagnostic tools, type of depression, and adjusted covariates were extracted from each eligible paper. Assessment of quality of each study was conducted using the 9-star Newcastle-Ottawa scale for observational studies (19). A quality score was awarded on the basis of 3 components: selection of participant (≤4 stars), comparability of the adjusted covariates (≤2 stars), and the ascertainment of the outcome measure (≤3 stars). Therefore, ≥6 points was determined as high quality (19).

Statistical analysis:

A meta-analysis was performed to compare homocysteine level in subjects with depression and healthy participants. Also, the association between hyperhomocysteinemia and risk of depression was included in the analysis. All Standard Errors were altered to Standard Deviations and then a random-effects model was used to estimate summary effect. Odds ratio, hazard ratio, and relative risk were used to detect the risk of depression. Heterogeneity between studies was assessed using I-squared (I^2) tests (I^2<50% was considered as acceptable heterogeneity). Pre-planned subgroup analysis was conducted to identify sources of heterogeneity. In subgroup analysis, studies were categorized by design, age, sex, method used to measure homocysteine, depression diagnostic tools, type of depression, adjusted covariates, and participants' health status. A fixed-effect model was used to measure heterogeneity between subgroups. Sensitivity analysis was conducted to determine the effect of each study or specific group of studies on the overall effect, whilst visual analysis of funnel plots was used to evaluate publication error. The symmetry of funnel plots was examined using Egger's regression

asymmetry test and Begg's rank correlation. All statistical analyses were performed using Stata software, and statistical significance was accepted at $p<0.05$.

Results:

Systematic review:

As shown in **Figure 1**, the primary search retrieved 2472 studies and were evaluated for inclusion and exclusion criteria. After duplicates were removed, we excluded 2256 articles because they were: *1)* unrelated to the topic, *2)* clinical trials or review articles, (*3)* experimental or *in vitro* studies, and 4) studies on subjects aged <18 years. Finally, 49 publications were eligible and included in the systematic review. Three articles did not report appropriate quantitative variables for pooling results in meta-analysis (13, 20, 21), and therefore, they were only included in systematic review.

Summary of the studies is described in Table 1. The design of 3 studies was prospective cohort, 22 articles were case-control, and 24 studies were cross-sectional, respectively. All studies were published from 2000 to 2020. Overall, in this meta-analysis, 46 studies (17, 22-66), which enrolled a total of 34873 participants (mean age=56.5 y), were included.

Quality assessment:

The 9-star Newcastle-Ottawa scale for observational studies was used to determine the quality of articles, where ≥6 points was determined to represent high quality(n=34 studies), whilst ≤6 was considered low quality (n=15)(67).

Meta-analysis:

Thirty-three studies compared homocysteine level in individuals with depression vs. healthy subjects. The overall effect size indicated that patients with depression had significantly higher homocysteine levels in comparison with healthy controls (WMD =2.53 µmol/L, 95% CI: 1.77, 3.30). Since the heterogeneity between studies was high (I^2=95.4%, $p<0.001$), a subgroup analysis was performed. Heterogeneity was partially attenuated when studies were stratified by depression diagnostic tool. As illustrated in **Figure 2**, meta-analysis showed that homocysteine level was significantly higher in subjects with depression in studies that used DSM-IV (WMD =3.10 µmol/L, 95% CI: 1.95, 4.26; I^2=95.0%), GDS (WMD =0.65 µmol/L, 95% CI: 0.03, 1.27; I^2=0.0%), ZDRS (WMD =2.28 µmol/L, 95% CI: 1.51, 3.04; I^2=0.0%), and BDI-II (WMD =1.39 µmol/L, 95% CI: 0.38, 2.41; I^2=0.0%) as the depression diagnostic tool, respectively. In contrast, there was no significant difference in homocysteine level in International Statistical Classification of Disease (ICD-10) (WMD =2.94

μmol/L, 95% CI: -0.35, 6.24; I^2=92.6%), Chines tool (WMD =3.42 μmol/L, 95% CI: -0.2, 7.05; I^2=95.8%), and "other" subgroups. Also, between subgroup heterogeneity was significant; however, additional subgroup analyses could not discern the source(s) of heterogeneity, as presented in **Table 2**.

Twenty-six studies reported the association between hyperhomocysteinemia and risk of depression. The overall effect size indicated that patients with hyperhomocysteinemia had a significantly higher risk of developing depression (pooled risk=1.34, 95% CI: 1.19, 1.52). Since the heterogeneity between studies was high (I^2=75.1%, p<0.001), subgroup analysis was performed. Heterogeneity was partially attenuated when studies were stratified by depression diagnostic tool. As reported in **Figure 3**, meta-analysis showed that patients with hyperhomocysteinemia had a significantly higher risk of depression in "DSM-IV" (pooled risk=1.77, 95% CI: 1.30, 2.40; I^2=84.8%), "GDS" (pooled risk=1.50, 95% CI: 1.20, 1.87; I^2=24.8%), and "other" subgroups (pooled risk=1.14, 95% CI: 1.03, 1.27; I^2=35.2%). In contrast, there was no association between hyperhomocysteinemia and risk of depression in ZDRS (pooled risk=0.94, 95% CI: 0.42, 2.09; I^2=0.0%) and PHQ (pooled risk=1.41, 95% CI: 0.7, 2.83; I^2=32.6%) subgroups. Although, when CESD was used as the depression diagnostic tool, participants with higher homocysteine levels were less likely to develop depression (effect size =0.71, 95% CI: 0.51, 1.00, I^2=0.00%). Further subgroup analyses which could not discern the heterogeneity are presented in **Table 3**.

Sensitivity analysis was conducted to determine the impact of each study or specific group of studies on the overall effect size. Results showed that removing individual studies did not change the overall effect size reported for homocysteine level and risk of depression.

A significant publication bias was observed for articles which compared homocysteine level in depressive subjects with healthy participants (P=0.088 for Begg's test and P<0.001 for Eggers's). Trim and fill analysis was performed and data were unchanged. No evidence supporting publication bias was found from studies reporting homocysteine level in relation to risk of depression (P=0.316 for Begg's test and P=0.643 for Eggers's).

Discussion:

This systematic review and meta-analysis indicated that homocysteine level was higher in subjects with depression in comparison with healthy controls. Also, participants with hyperhomocysteinemia had increased odds of developing depression. However, the tools used to diagnose and evaluate depression were significant in determining this relationship.

In this study, we included both unadjusted and full-adjusted studies to compare their findings. In contrast to unadjusted studies, pooling full-adjusted studies showed a significant association between risk of depression and serum homocysteine concentration. This finding showed the importance of confounders such as smoking status, BMI, physical activity, dietary intakes, alcohol, daily vitamin B12 and folate supplements adjusted in full-adjusted studies (25, 48). Therefore, the results of unadjusted studies may not be reliable.

A previous systematic review supports the finding that hyperhomocysteinemia has a possible pathophysiological role in depression; indeed, strong evidence for a link between homocysteine level and depression, vascular diseases, and neurotransmitters was reported (68). in addition, similar to the current meta-analysis, a previous review article reported an increase in homocysteine levels in approximately one-third of patients with depression (69). Hyperhomocysteinemia is manifested from folate and cobalamin deficiency, and the association between these nutrients and depression has been reported in several studies. However, it is unclear whether homocysteine is directly involved in the development of depression; moreover, homocysteine is not necessarily regarded as necessarily an indication of folate and cobalamin deficiency.

There is a two-sided association between hyperhomocysteinemia and depression, i.e., hyperhomocysteinemia has a possible pathophysiological role in depression and depression-induced anorexia can cause hyperhomocysteinemia (70). Most of the studies included in this meta-analysis were retrospective and the number of prospective studies was low. Retrospective studies have demonstrated that people with hyperhomocysteinemia are more likely to develop depression. On the other hand, the results of prospective studies are contradictory. Therefore, causal directionality between depression and hyperhomocysteinemia is unclear, and more prospective studies are needed.

Hyperhomocysteinemia can be caused by genetic and non-genetic factors, including impaired remethylation of homocysteine due to insufficient dietary absorption or intake of pyridoxine, cobalamine and folate, enzyme deficiency (e.g., Methyl Tetra Hydro Folate Reducase and Cystathionine-Beta-Synthetase), some medications (e.g., nitrous oxide , methotrexate , antielpileptics), and unhealthy lifestyle (e.g., smoking) (11). There is a well-known relationship between hyperhomocysteinemia and depression (5, 45). Hyperhomocysteinemia can inhibit neurotransmitters and alter their activity, which may result in depression (10); in addition, oxidative stress, mitochondrial dysfunction, and apoptosis in dopaminergic neurons caused by hyperhomocysteinemia may also lead to depression (71). Homocysteine is an intermediate of methionine metabolism converted to S-

adenosylmethionine (SAM) in the presence of cobalamin and folate. SAM has antidepressant properties and acts as a tricyclic antidepressant in the treatment of depression. Finally, SAM converts to S-adenosylhomocysteine (SAH), where SAH-hydrolase catalyzes interconversion of SHA and homocysteine. Therefore, in hyperhomocysteinemia, SAH-hydrolase acts in an opposing manner and increases conversion of homocysteine to SHA. SAH is a potent competitive inhibitor of SAM-dependent methyltransferase in the brain, and thus, SAM hypomethylation impairs brain function and increases the risk of depression (11). Also, hyperhomocysteinemia leads to activation of the glutamate receptor N-methyl-D-asparte, and subsequently increases cytoplasmic calcium. Activation of these receptors causes the accumulation of reactive oxygen species and neurotoxicity, which can, ultimately, cause brain damage and depression(72).

In the present study, subgroup analysis showed that depression diagnostic tool was a source of heterogeneity. DSM-IV and ICD-10 are the most widely used depression diagnostic tools (73); studies that used Center for Epidemiological Studies-Depression (CESD) as a depression diagnostic tool showed that participants with higher homocysteine level were less likely to develop depression, whilst other studies reported conflicting results. The CESD scale is a 20-item self-report tool that measures depressive symptoms (74, 75). This scale has a score ranged from 0 to 60 and subjects are categorized as depressed with score $\geq$ 16. Some studies suggested that using CESD results in false positive diagnoses of depression and this cut off may be too low for some older adults. Therefore, it may categorize healthy subjects as depressed (76-78). It is possible that studies that used CESD misdiagnosed healthy subjects as patients with depression, and therefore, the observed protective effect of hyperhomocysteinemia should be interpreted with caution.

The current meta-analysis has some limitations: *1*) most of the included studies had a cross-sectional design, therefore, cause and effect could not be determined, *2*) measurement of homocysteine was varied between studies, which could have conceivablyinfluenced the results, and *3*) the type or severity of depression was not reported in most included studies, thus, we could not evaluate the effect of homocysteine on different types of depression. Notwithstanding the aforementioned limitations, the present study has strengths that should be acknowledged. Indeed, we followed stringent systematic review and Meta analyses guidelines (PRISMA), and ensured that several databases were searched to attain the best available evidence. Furthermore, comprehensive, pre-defined, subgroup analyses were performed, which enabled us to highlight the influence type of depression diagnostic tool has, which, to the authors knowledge, has not previously be reported.

Conclusion

In conclusion, the current systematic review and meta-analysis showed that hyperhomocysteinemia is positively associated with the risk of depression, however, the tool used for diagnosis of depression has a major influence and thus, future studies should focus on the tools for depression assessment.

Acknowledgments

Financial support: The study was supported by Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran. And approved by code 16830. M.H.R and F.M designed the study and searched databases and performed data analysis. F.M and M.A screened studies and extracted data. M.H.R and F.M and K.L and C.C contributed to the writing and revising of the manuscript.

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Table 1 Characteristics of included studies

Author (Country/Year)	Number of subjects (Female/ Male)	Mean age (years)	design	Duration (year)	Comorbidity (Yes/No)	Homocysteine tool	Depression tools/type 0f depression	Adjusted variables	result	score
Penninx (2000/ US)	700 (700/0)	77.3	cross-sectional	-	No	HPLC	GDS	Unadjusted	No difference between patients with depression vs. healthy	6
Bottiglieri (2000/ UK)	84 (47/37)	46.6	case control	-	No	HPLC	DSM-IV	Unadjusted	Higher Homocysteine in patients with depression VS. healthy	5
Tiemeier (2002/ Netherlands)	694 (NR)	72.9	cross-sectional	-	No	HPLC	DSM-IV	Full-adjusted	↑OR of depression	8
Tallova (2003/ Czech Republic)	28 (28/0)	39.5	case control	-	No	HPLC	ICD 10	Unadjusted	Higher Homocysteine in patients with depression VS. healthy	5
Bjelland (2003/ Norway)	5948 (2558/ 2291)	59.6	cross-sectional	-	No	HPLC	HADS	Full-adjusted	↑OR of depression	8
Kelly (2004/ UK)	189 (114/75)	49	case-control	-	No	HPLC	ICD-10 criteria	Semi-adjusted	No difference between patients with depression vs. healthy	5
Panagiotakos (2004/ Greece)	853 (400/453)	44.5	cross-sectional	-	yes	NR	ZDRS	unadjusted	Higher Homocysteine in patients with depression	7

									VS. healthy	
Tolmunen (2004/ Finland)	924 (0/924)	56.4	cross-sectional	-	No	HPLC	18-item Human Population Laboratory Depression Scale	Unadjusted	Higher Homocysteine in patients with depression VS. healthy	6
Chen (2005/ Taiwan)	59 (40/19)	71.75	case control	-	No	immunoassay	DSM-IV/ MDD	Full-adjusted	Higher Homocysteine in MDD VS. healthy	6
Sachdev (2005/ Australia)	412 (201/ 211)	62.54	cross-sectional	-	No	HPLC	PHQ	Full-adjusted	No difference between patients with depression vs. healthy	8
Refsum (2006/ Norway)	7,053 (NR)	53.5	cohort	4-7	No	HPLC	HADS-D	Semi-adjusted	↑OR of depression	7
Almeida (2007/ Australia)	5,439 (0/5439)	80	cross-sectional	-	No	immunoassay	GDS-15	Unadjusted	↑OR of depression	7
Clement (2007/ US)	73 (31/42)	60	cross-sectional	-	yes	immunoassay	BDI-II	Unadjusted	No difference between patients with depression vs. healthy	6
Dimopoulos (2007/ Greece)	66 (40/26)	65.6	case control	-	No	immunoassay	DSM-IV	Unadjusted	Higher Homocysteine in patients with depression VS. healthy	5
Kamphuis (2007/ Netherlands)	332 (0/332)	80	case control	-	No	NR	ZDRS	Full-adjusted	↔OR of depression	7
Frieling (2008/ Germany)	44 (44/0)	26.2	cross-sectional	-	yes	HPLC	DSM-IV/ MDD	Unadjusted	Higher Homocysteine in MDD VS. healthy	6

									↑OR of depression	
Ipcioglu (2008/ Turkey)	78 (38/40)	29.6	case control	-	No	HPLC	DSM-IV	Unadjusted	Higher Homocysteine in patients with depression VS. healthy	5
Kim (2008/ Korean)	732 (432/300)	72.8	cross-sectional	-	No	HPLC	GMS /late life depression	Full-adjusted	↑OR of depression	8
Yuan (2008/ China)	196 (138/58)	65	case control	-	Yes	capillary electrophoresis with ultraviolet detection	DSM-IV / GD	Unadjusted	Higher Homocysteine in MDD VS. healthy ↑OR of depression	5
Ng (2009/ Singapore)	669 (414/255)	65.2	Cross-sectional	-	No	immunoassay	GDS	Full-adjusted	No difference between patients with depression vs. healthy ↔OR of depression	8
Alexopoulos (2010/ Germany)	65 (48/17)	70.95	case control	-	No	immunoassay	DSM-IV /G D	Unadjusted	No difference between patients with depression vs. healthy	5
Beydoun (2010/ US)	2524 (1444/1080)	52.5	cross-sectional	-	No	Abbott Homocysteine (HOMOCYSTEINE) assay	PHQ	Full-adjusted	↔OR of depression	7
Chen (2010/ Taiwan)	83 (65/18)	78.1	cross-sectional	-	Yes	HPLC	National Institute of Mental Health provisional diagnostic criteria /MDD	Unadjusted	No difference between patients with depression vs.	6

									healthy	
El-Batch1 (2010/ Egypt)	80 (48/32)	61.4	case control	-	No	ELISA	DSM-IV	Full-adjusted	Higher Homocysteine in patients with depression VS. healthy	6
Forti (2010/ Italy)	457 (217/ 240)	≥65	cohort	4	No	immunoassay	DSM-IV	Full-adjusted	Higher Homocysteine in patients with depression VS. healthy ↓OR of depression	8
Nanri (2010/ Japan)	530 (217/ 313)	44	cross-sectional	-	No	HLPC	CESD	Full-adjusted	↑OR of depression	8
Qiu (2010/ US)	1058 (805/253)	75.3	cross-sectional	-	No	HLPC	DSM-IV / late life depression	Unadjusted	Higher Homocysteine in late life depression VS. healthy	6
Watanabe (2010/ Japan)	86 (86/0)	30.9	cross-sectional	-	No	HPLC	CESD	Unadjusted	No difference between patients with depression vs. healthy ↔OR of depression	6
Chatterjee (2010 /UK)	127 (51/76)	70	case control	-	yes	-	DSM-IV/ PSD	Full-adjusted	Higher Homocysteine in patients with depression VS. healthy	7
Yapislar (2012/ Turkey)	38 9/8 10/10	36	case control	-	Yes	HPLC	DSM-IV/ MDD	Unadjusted	Higher Homocysteine in MDD VS. healthy	5

Almeida (2012/ Australia)	3687 (0/3687)	78	cross-sectional	-	no	immunoassay	GDS-15	Full-adjusted	↑OR of depression	8
Ebesunun (2012/ Nigeria)	60 (21/9) case NR (control)	40.2	case control	-	No	immunoassay	ICD-10 /MDD	Unadjusted	Higher Homocysteine in MDD VS. healthy	5
Aishwarya (2013/ India)	103 (103/0)	≤30	case control	-	No	ELISA	EPDS / PPD	Unadjusted	Higher Homocysteine in PPD VS. healthy	5
Nabi (2013/ France)	3392 (1789/1603)	50.5	cross-sectional	-	No	HLPC	DSM-IV / MDD	Full-adjusted	↑OR of depression	8
Kitzlerová (2014/ Prague)	85 NR	75.6	case control		yes	HPLC	GDS	Semi-adjusted	Higher Homocysteine in patients with depression VS. healthy	5
Lok (2014/ Netherlands)	210 (152/58)	45.55	case control	-	No	HLPC	DSM IV /MDD	Full-adjusted	Higher Homocysteine in MDD VS. healthy	6
Narayan (2014/ India)	120 (64/56)	29.6	case control	-	yes	immunoassay	ICD10	Semi-adjusted	Higher Homocysteine in patients with depression VS. healthy	5
Vargas (2014/Brazil)	342 (226/116)	39	cross-sectional	-	No	immunoassay	DSM-IV/HDRS	Full-adjusted	No difference between patients with depression vs. healthy	8
Jianxi (2015/ China)	74 (74/0)	40	case control	-	No	immunoassay	-Chinese Classification of Mental Disorder / PPD	Unadjusted	Higher Homocysteine in PPD VS.	4

									healthy	
Tang (2015/ China)	226 (102/124)	66	cross-sectional	-	Yes	NR	DSM-IV / PSD	Full-adjusted	Higher Homocysteine in patients with depression VS. healthy ↑OR of depression	6
Wang (2015/ China)	865 (462/403)	70.13	cross-sectional	-	Yes	NR	ZDRS	Unadjusted	Higher Homocysteine in patients with depression VS. healthy	6
Wei-wei (2015/ China)	179 (62/117)	63.9	case control	-	Yes	enzymatic cycling assay	Chinese classification	Unadjusted	Higher Homocysteine in patients with depression VS. healthy	5
Cheng (2017/ China)	259 (129/130)	60	cohort	1	yes	NR	DSM-IV/ PSD	Full-adjusted	↑OR of depression	8
Elstgeest (2017/ Netherlands)	1205 (621/584)	74.6	Cohort	-	No	immunoassay	CESD	Full-adjusted	↔OR of depression	8
Li (2017/ China)	238 (119/119)	63.5	case control	-	yes	NR	DSM-IV / PSD	Full-adjusted	Higher Homocysteine in PSD VS. healthy ↑OR of depression	6
Enko (2018/ US)	238 (157/81)	41.5	Case-control	-	yes	immunoassay	BDI-II/ MDD	Unadjusted	Higher Homocysteine in MDD VS. healthy	5
Yin (2018/ China)	598 (182/41	60.73	cross-sectional	-	Yes	enzymatic cycling assay	DSM-IV	Full-adjusted	No difference between	8

	6)								patients with depression vs. healthy ↔OR of depression	
Xu	333 (152/181)	64	cross-sectional	-	Yes	standard laboratory methods	BDI-FS/ PSD	Full-adjusted	↑OR of depression	8
sarawathy (2019/ India)	303 (NR)	45	cross-sectional	-	No	immunoassay	PHQ	Full-adjusted	↑OR of depression	8

HPLC: high-performance liquid chromatography, GDS: Geriatric Depression Scale, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV, ICD-10:International Statistical Classification of Disease , HADS :Hospital Anxiety and Depression Scale , NR: not reported, ZDRS :Zung Self-Rating Depression Scale, MDD: Major Depressive Disorder, PHQ :Patient Health Questionnaire, BDI-II: Beck Depression Index II, GMS: Geriatric Mental State Schedule, GD: Geriatric Depression, ELISA : Enzyme linked ImmunoSorbent Assay, CESD: Center for Epidemiologic Studies Depression Scale, PSD: post-stroke depression, PPD: postpartum depression, HRSD :Hamilton Rating Scale of Depression

Table 2: Subgroup analysis to compare serum level of homocysteine in patients with depression and healthy subjects

Variable		**Study (n)**	**weight mean difference**	I^2	**P** (within subgroup heterogeneity)	**P** (between subgroup heterogeneity)
Adjustment	Unadjusted	21	3.48 (2.38, 4.58)	93%	<0.001	<0.001
	Full adjusted	10	1.17 (0.37, 1.96)	89.6%	<0.001	
	Semi adjust	2	0.49 (3.21, 4.19)	84.4%	0.024	
Age	Adult	30	2.66 (1.83, 3.48)	95.7%	<0.001	0.785
	Elderly	3	0.68 (0.90, 2.26)	70%	0.036	
Comorbidity	Yes	20	1.86 (1.16, 2.57)	92%	<0.001	<0.001
	No	13	3.35 (2.06, 4.64)	89.6%	<0.001	
Depression tools	DSM-IV	15	3.10 (1.95, 4.26)	95%	<0.001	<0.001
	GDS	2	0.65 (0.03, 1.27)	0%	0.538	
	Others	5	1.13 (-0.04, 2.29)	73.3%	0.005	
	ICD-10	4	2.94 (-0.35, 6.24)	92.6%	<0.001	
	ZDRS	3	2.28 (1.51, 3.04)	0%	0.469	
	BDI-II	2	1.39 (0.38, 2.41)	0%	0.729	
	Chinese classification	2	3.42 (-0.20, 7.05)	95.8	<0.001	
Type 0f depression	NR	21	2.10 (1.14, 3.05)	93.2%	<0.001	<0.001
	MDD	5	4.35 (1.39, 7.31)	95.9%	<0.001	
	Late life depression	1	-0.20 (-1.14, 0.74)	-	-	
	GD	2	4.17 (2.14, 6.20)	40%	0.197	
	PPD	2	2.53 (0.17, 4.88)	66.4%	0.085	
	PSD	2	4.17 (1.01, 7.34)	86.6%	0.006	
Sex	Both	23	3.06 (1.93, 4.20)	96.5	<0.001	<0.001
	Female	7	1.73 (0.70, 2.76)	82.8	<0.001	
	Mal	3	1.04 (0.50, 1.58)	0	0.870	
Homocysteine tool	HPLC	12	1.91 (0.90, 2,91)	92.8	<0.001	<0.001
	NR	5	3.00 (1.55, 4.44)	77.1	0.002	
	Immunoassay	11	2.30 (1.11, 3.50)	88.5	<0.001	

	Others	1	4.90 (3.34, 4.46)	-	-	
	ELISA	2	3.07 (1.89, 4.30)	0	0.402	
	Enzymatic cycling assay	2	2.72 (-2.25, 7.69)	97.9%	<0.001	
Overall		33	2.53 (1.77, 3.30)	95.4	<0.001	

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV, GDS: Geriatric Depression Scale, ICD-10:International Statistical Classification of Disease, ZDRS: Zung Self-Rating Depression Scale, BDI-II: Beck Depression Index II, NR: not reported, MDD: Major Depressive Disorder, GD: Geriatric Depression, PPD: postpartum depression, PSD: post-stroke depression, HPLC: high-performance liquid chromatography, ELISA : Enzyme linked ImmunoSorbent Assay

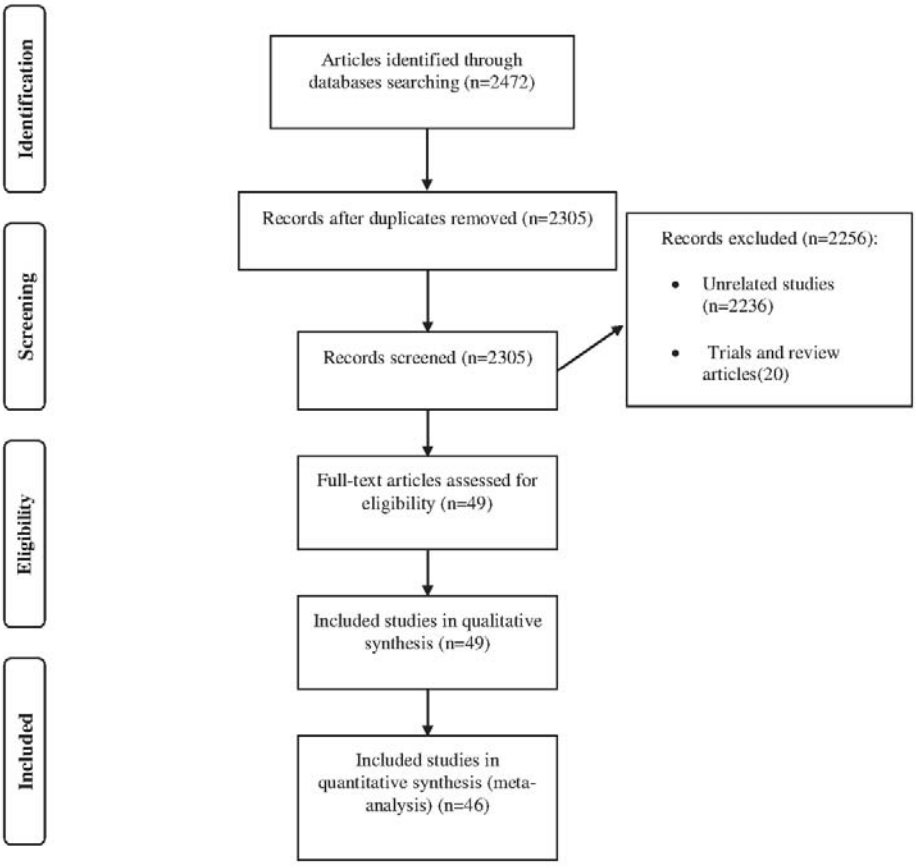
Table 3: Subgroup analysis to assess the association between serum level of homocysteine and risk of depression

Variable		Study (n)	Effect size	I^2	**P** (within subgroup heterogeneity)	**P** (between subgroup heterogeneity)
Adjustment	Unadjusted	3	1.50 (0.67, 3.34)	61.8%	0.073	0.015
	Full adjusted	23	1.33 (1.17, 1.51)	75.3%	<0.001	
Age	Adult	22	1.35(1.18, 1.55)	75.4%	<0.001	0.012
	Elderly	4	1.27 (0.89, 1.82)	65.6%	0.033	
Comorbidity	Yes	6	1.55 (1.24, 1.93)	90.1%	<0.001	0.002
	No	20	1.25 (1.06, 1.47)	53.2%	0.003	
Depression tools	DSM-IV	11	1.77 (1.30, 2.40)	84.8%	0.000	<0.001
	GDS	3	1.50 (1.20, 1.87)	24.8%	0.264	
	CESD	5	0.71 (0.51, 1.00)	0%	0.966	
	Others	3	1.14 (1.03, 1.27)	35.2%	0.213	
	ZDRS	1	0.94(0.42,2.09)	0%	0.000	
	PHQ	3	1.14(0.70,2.83)	32.6%	0.227	
Type 0f depression	NR	17	1.26 (1.03, 1.54)	49.1%	0.012	0.009
	MDD	4	1.35 (0.82, 2.20)	73.5%	0.010	
	Late life depression	1	1.25 (1.04, 1.50)	-	-	
	PSD	4	1.52 (1.20, 1.93)	93.5%	<0.001	
Design	Case-control	3	2.06 (0.75, 5.65)	88.5%	<0.001	<0.001
	Cross-sectional	18	1.23 (1.11, 1.36)	52.6%	0.05	
	Cohort	5	1.58 (0.79, 3.17)	85.8%	<0.001	
Sex	Both	14	1.33 (1.16, 1.52)	80.2%	<0.001	0.004
	Female	6	1.19 (0.59, 2.41)	75.5%	0.001	
	Male	6	1.60 (1.31, 1.97)	0%	0.674	
Homocysteine Tool	HPLC	9	1.18 (0.93, 1.49)	46.1%	0.062	0.001
	NR	4	2.02 (0.98, 4.17)	92.8%	0.000	
	Immunoassay	9	1.42 (1.07, 1.88)	67.2%	0.002	
	Enzymatic cycling	1	1.41 (0.092, 2.17)	-	-	

	assay					
	Others	3	1.09 (1.05, 1.13)	0%	0.748	
Overall		26	1.34 (1.19, 1.52)	75.1%	<0.001	

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV, GDS: Geriatric Depression Scale, CESD: Center for Epidemiologic Studies Depression Scale, ZDRS: Zung Self-Rating Depression Scale, PHQ: Patient Health Questionnaire NR: not reported, MDD: Major Depressive Disorder, PSD: post-stroke depression, HPLC: high-performance liquid chromatography

Figure 1



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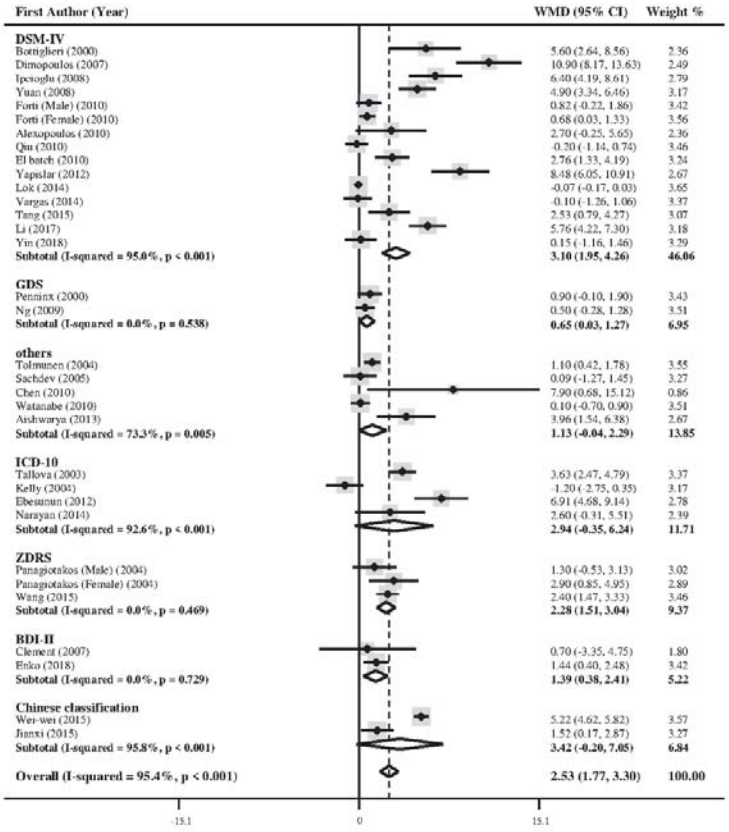

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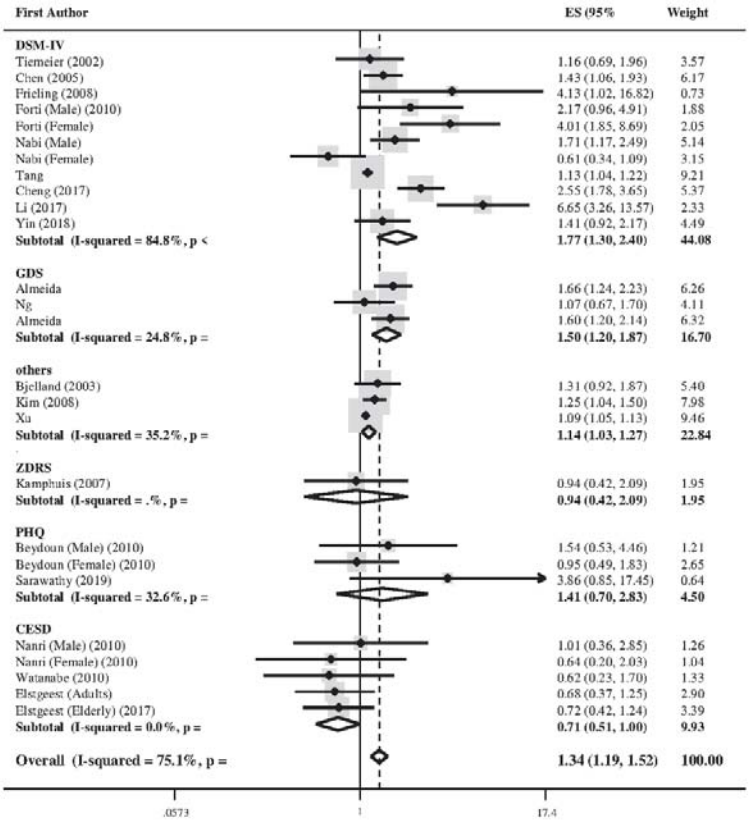

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