Zinc in Depression: A Meta-Analysis

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Background: Zinc is an essential micronutrient with diverse biological roles in cell growth, apoptosis and metabolism, and in the regulation of endocrine, immune, and neuronal functions implicated in the pathophysiology of depression. This study sought to quantitatively summarize the clinical data comparing peripheral blood zinc concentrations between depressed and nondepressed subjects.

Methods: PubMed, Cumulated Index to Nursing and Allied Health Literature, and PsycINFO were searched for original peer-reviewed studies (to June 2012) measuring zinc concentrations in serum or plasma from depressed subjects (identified by either screening or clinical criteria) and nondepressed control subjects. Mean (±SD) zinc concentrations were extracted, combined quantitatively in random-effects meta-analysis, and summarized as a weighted mean difference (WMD).

Results: Seventeen studies, measuring peripheral blood zinc concentrations in 1643 depressed and 804 control subjects, were included. Zinc concentrations were approximately −1.85 μmol/L lower in depressed subjects than control subjects (95% confidence interval: [CI]: −2.51 to −1.19 μmol/L, $Z_{17} = 5.45$, $p < .00001$). Heterogeneity was detected ($\chi^2_{17} = 142.81$, $p < .00001$, $I^2 = 88\%$) and explored; in studies that quantified depressive symptoms, greater depression severity was associated with greater relative zinc deficiency ($B = -1.503$, $t_9 = -2.82$, $p = .026$). Effect sizes were numerically larger in studies of inpatients (WMD −2.543, 95% CI: −3.522 to −1.564, $Z_9 = 5.09$, $p < .0001$) versus community samples (WMD −.943, 95% CI: −1.563 to −.323, $Z_7 = 2.98$, $p = .003$) and in studies of higher methodological quality (WMD −2.354, 95% CI: −2.901 to −1.807, $Z_7 = 8.43$, $p < .0001$).

Conclusions: Depression is associated with a lower concentration of zinc in peripheral blood. The pathophysiological relationships between zinc status and depression, and the potential benefits of zinc supplementation in depressed patients, warrant further investigation.

Key Words: Depression, depressive symptoms, major depressive disorder, micronutrient, trace metal, zinc

Major depressive disorder (MDD) is a chronic condition, characterized by high rates of relapse and relatively low rates of remission, despite treatment with available antidepressant therapies. Moreover, it is increasingly appreciated that the syndrome of MDD is associated with ancillary health risks such as cardiovascular and endocrine comorbidities, psychiatric symptoms that linger between episodes, and the phenomenon of "neuroprogression" whereby cognitive function can be affected and future episodes can become more numerous and severe (1). Further investigation is required to identify factors of potential pathophysiological relevance to suggest alternative or adjunctive strategies for treatment.

A growing body of evidence demonstrates that experimental zinc deficiency can induce depressive-like behavior in animals, which can be effectively reversed by zinc supplementation (2,3). Zinc can also produce antidepressant-like effects in preclinical models of depression (4,5), acting additively with monoaminergic antidepressants (6,7). Moreover, zinc deficiency can interfere with antidepressant response in the tail suspension test (3). Preliminary clinical trials have suggested that zinc added to antidepressant treatment might result in more rapid or more effective symptomatic improvement (8); however, the basis for these findings remains unclear, and the clinical significance of zinc deficiency remains largely unqualified.

Zinc status is most frequently assessed by assaying zinc concentrations from serum or plasma (9). Peripheral blood zinc concentrations have been measured in numerous studies of depressed and nondepressed subjects over the past several decades. Many (10–14) but not all (15–17) of these studies suggest that depression might be associated with lower zinc concentrations in various population samples. The present meta-analysis was undertaken to determine whether the clinical evidence collectively supports lower zinc concentrations in the blood of depressed patients as compared with healthy nondepressed control subjects and to estimate the magnitude of this difference. In addition, heterogeneity in these findings was explored to suggest factors that might influence this effect, such as age, gender, depressive symptom severity, clinical setting, and study quality.

Methods and Materials

Data Sources

Methodology was consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (18). The MEDLINE, Embase, the Cochrane Collaboration, Allied and Complementary Medicine Database, and Cumulated Index to Nursing and Allied Health Literature were searched up to June 2012. A sample search strategy (for PubMed, National Library of Medicine) is detailed in Supplement 1. Reference lists of retrieved studies were searched for additional reports.

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Study Selection

Inclusion criteria were: 1) studies measuring serum or plasma zinc concentrations; 2) inclusion of a depressed group as diagnosed by standard recognized criteria or screened with a standardized instrument; and 3) inclusion of a medically healthy nondepressed comparison group. Studies were excluded if they reported on depressive symptoms in the context of other neuropsychiatric disorders (e.g., schizophrenia, bipolar disorder, autism), medical illnesses (e.g., coronary artery disease, cancer), or conditions (e.g., pregnancy, postpartum period).

Data Extraction

Two independent raters examined each article for eligibility, results were compared between raters, and any disagreements regarding inclusion were settled by consensus with a third rater. The methods and results sections of each relevant article were analyzed. Serum or plasma zinc concentrations (mean ± SD) were extracted for depressed and control subjects. Missing data were requested from the corresponding author of the publication. Population characteristics (mean age, percentage female, proportion with an antidepressant and mean depressive symptom severity) and study variables (inclusion criteria and diagnosis method, clinical context, and the like) were extracted.

Statistical Analyses

Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated with a random effects model (19). Random effects models assume and account for variable underlying effects in estimates of uncertainty, including both within-study and between-studies variance, and they are preferable if heterogeneity is expected on the basis of study variables. Effect sizes were determined with Stata software (release 10.1, StataCorp, College Station, Texas).

Heterogeneity among combined results was evaluated with a Q statistic, calculated in χ^2 analysis. A significant Q statistic indicates diversity in the characteristics of the combined trials. Inconsistency was assessed with an I^2 index (20), to determine the impact of heterogeneity. To identify potential sources of heterogeneity, subgroup analyses were carried out on the basis of clinical setting (subgroups of inpatient studies and community samples), depression criteria used to classify subjects (a diagnosis with a structured clinical interview vs. a screening instrument), studies where patients and control subjects were matched for age and gender, and studies that explicitly excluded any antidepressant use. Study level inverse variance weighted meta-regression analyses were conducted to investigate relationships between WMDs and population characteristics (e.g., mean age, proportion female, depressive symptom severity). Because different scales were used to quantify symptom severity, mean values were considered relative to standard cutoffs for each scale (21–23). Regression data were summarized with unstandardized regression coefficients (*B*) and 95% CIs.

Risk of publication bias was assessed visually with funnel plots and quantitatively with Egger's test (24,25). Study quality items were assessed with items from the Newcastle Ottawa Scale and the Cochrane Collaboration's risk of bias assessment tool, addressing key methodological criteria relevant to included studies. Stata software was used for meta-regression, subgroup and bias analyses.

Results

Characteristics of Included Studies

Search criteria identified 299 unique records, of which 23 studies met inclusion criteria (Figure 1). Data could be extracted from 15 studies, and the authors of 2 additional studies provided means and SDs (14,15). The characteristics of the included studies are summarized in Table 1. Of those studies, 10 reported on psychiatric inpatients, whereas 7 reported on community samples. The included studies ranged in sample size from 13 to 328, including a total of 1643 depressed patients and 804 nondepressed control subjects. Among the included subjects, 34.45% were male and the mean age was 37.7 years.

Zinc Concentrations in Depressed and Control Subjects

Mean peripheral blood zinc concentrations were lower by approximately 1.85 μmol/L in depressed subjects compared with control subjects (95% CI: −2.51 to −1.19, $Z_{17} = 5.45$, $p < .00001$) (Figure 2). Heterogeneity was detected in this comparison ($\chi^2_{17} = 142.81$, $p < .00001$, $I^2 = 88\%$).

Assessment of Bias

A funnel plot and Egger's test revealed potential risk of publication bias ($t_{17} = -3.31$, $p = .004$). Items that might have contributed to risk of bias in each study are presented in Table S1 in Supplement 1 and explored further in the following sections.

Exploration of Heterogeneity and Risk of Bias

Gender and Gender-Matching. The effect sizes did not vary on the basis of the proportion of male and female subjects in the studies by meta-regression ($B = -.001047$, $t_{15} = .007$, $p = .942$). In studies that explicitly matched patients and control subjects for gender, heterogeneity ($I^2 = 86.4\%$) and overall effect size (WMD = −1.484, 95% CI = −2.146 to −.822, $Z_{13} = 4.39$, $p < .0001$) were similar to those of the whole group, although the risk of bias was attenuated ($t_{13} = -2.16$, $p = .052$).

Age and Age-Matching. In studies that explicitly matched patients and control subjects for age, heterogeneity ($I^2 = 82.9\%$) and overall effect size ($WMD_{11} = -1.767$, 95% CI: −2.447 to −1.087, $Z_{12} = 5.09$, $p < .0001$) were similar to those among all studies; however, risk of bias within this subgroup was not detected ($t_{12} = -1.67$, $p = .123$). Effect sizes did not vary on the basis of the mean age of participants in meta-regression analysis ($B = -.0018014$, $t_{13} = .06$, $p = .956$).

In a subgroup of studies with mean ages between 25 and 65 (excluding predominantly younger and geriatric populations and populations of unknown mean age), the effect size (WMD = −1.664, 95% CI: −2.390 to −.938, $Z_{11} = 4.49$, $p < .00001$) and heterogeneity ($I^2 = 87.4\%$) were comparable to those for the whole group, and the risk of bias persisted ($t_{11} = -2.29$, $p = .045$).

Antidepressant Use

There was no association between effect size and the proportion of patients using an antidepressant in meta-regression analysis ($B = -.02433$, $t_9 = 1.05$, $p = .323$). Effect sizes varied between studies that excluded antidepressant use (WMD = −2.838, 95% CI: −4.048 to −1.629, $Z_7 = 4.60$, $p < .00001$, $I^2 = 90.2\%$), those that reported the proportion of patients using an antidepressant (WMD = −1.238, 95% CI: −2.199 to −.277, $Z_1 = 2.52$, $p = .012$, $I^2 = 43.3\%$), and those that did not report antidepressant use (WMD = −1.027, 95% CI: −1.846 to −.207, $Z_7 = 2.46$, $p = .014$, $I^2 = 81.8\%$). The risk of bias was attenuated in the subgroup that did not report antidepressant use ($t_7 = -1.55$, $p = .172$) but not in the subgroup that excluded antidepressants ($t_7 = -3.28$, $p = .017$).

Clinical Setting

In studies reporting on populations of psychiatric inpatients, the overall effect size was numerically larger (WMD −2.543, 95%

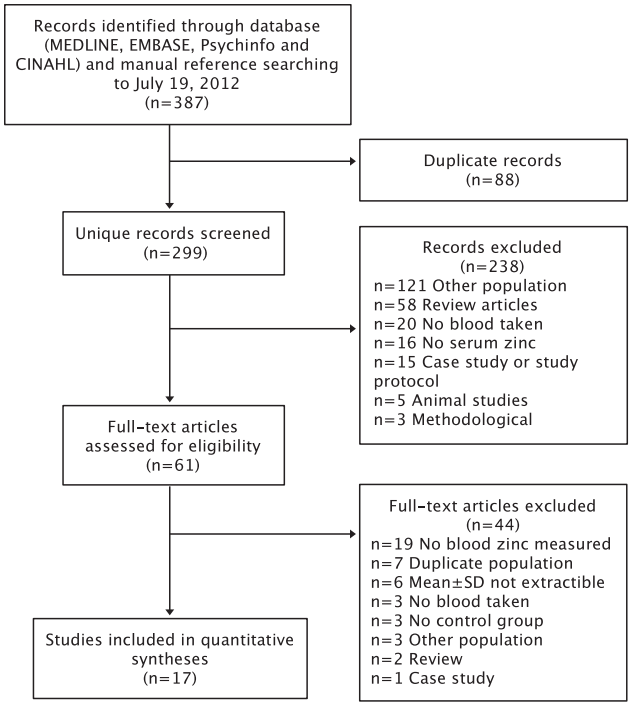

Figure 1. Search results and study selection.

CI: −3.522 to −1.564, $Z_9 = 5.09$, $p < .0001$), but the heterogeneity was unchanged ($I^2 = 82.7\%$). Among community samples the effect size was smaller (WMD −.943, 95% CI: −1.563 to −.323, $Z_7 = 2.98$, $p = .003$), and heterogeneity persisted ($I^2 = 79.2\%$). Risk of bias was not significant among subgroups of inpatient and community studies ($t_9 = -.54$, $p = .606$; and $t_7 = -2.32$, $p = .060$, respectively).

Depression Severity

In studies that reported depressive symptom severity with a continuous scale, greater mean depressive symptom severity was associated with greater differences in zinc between depressed patients and control subjects by meta-regression (Figure 3). This association was significant when controlling for clinical setting ($B = -1.505$, $t_8 = -2.58$, 95% CI: −2.932 to −.079, $p = .042$), but the difference between inpatient studies versus community samples was not ($B = -.051$, $t_8 = -.07$, 95% CI: −1.826 to 1.723, $p = .946$).

Diagnostic Methodology

Effect sizes (WMD −2.271, 95% CI: −3.573 to −.969, $Z_7 = 3.42$, $p = .001$) and heterogeneity ($I^2 = 90.9\%$) were numerically larger in studies that used a self-report instrument to screen for depression compared with those that used a structured interview for diagnosis (WMD −1.653, 95% CI: −2.425 to −.881, $Z_9 = 4.20$, $p < .0001$; $I^2 = 84.8\%$). Risk of bias was not detected among studies that used a diagnostic interview ($t_9 = -1.06$, $p = .319$), but it was significant among studies that relied on a self-report inventory ($t_7 = -5.09$, $p = .002$).

Overall Study Quality

In a subgroup of studies that satisfied the majority of risk of bias and study quality items (Supplement 1), the overall effect was significant (WMD −2.354, 95% CI: −2.901 to −1.807, $Z_7 = 8.43$, $p < .0001$), and heterogeneity was nonsignificant ($I^2 = 43.5\%$, $p = 0.088$). In the other studies, the mean difference remained significant (WMD −1.395, 95% CI: −2.228 to −.562, $Z_9 = 3.28$, $p < .001$), and heterogeneity persisted ($I^2 = 88.4\%$, $p < .001$).

Discussion

The present meta-analysis reports the concentration of zinc in the peripheral blood of depressed patients to be approximately 1.850 μmol/L lower than that of control subjects. Most of the included studies reported the means of depressed and control groups to be within normal laboratory reference ranges (i.e., 10.1–16.8 μmol/L) (35); however, the depressed group means were often near the lower boundary of the normal range.

Some variation in peripheral blood zinc concentrations might be explained by depressive symptom severity. In our meta-regression analysis, studies that reported higher mean depressive symptoms found larger effect sizes. Individual studies noted similar relationships; specifically, one study found lower serum zinc in major versus minor depressed patients (13), whereas others found lower zinc in association with greater depressive symptom severity (10,13,14,26,36) or in treatment-resistant or melancholic patients (14,37). Because symptom severity was related to zinc concentrations, combining relatively small studies of psychiatric inpatients with larger studies of community samples might have biased the summary estimate toward the smaller effect size that would be expected in less severely depressed subjects.

Among included studies there were no differences in effect size on the basis of the proportion of male versus female subjects; however, gender differences revealed in some of the included studies are noteworthy. In two studies, the zinc concentrations of depressed women were lower than those of depressed men (12,13). Other studies found associations between zinc intake (38) or copper/zinc ratios (17) and depression that were restricted to women, whereas age-related decreases in zinc concentrations (39) and increases in zinc deficiency (40) were found only in men. Our meta-regression analyses did not reveal an effect of age among the included studies, although van Kempen *et al.* (11) reported lower zinc concentrations in depressed patients older than 65 years of age than in younger depressed patients.

Although association studies cannot determine the direction of causation, a causal association between zinc status and depression is biologically plausible. Zinc has antioxidant properties, helps to maintain endocrine homeostasis and immune function, and plays multiple roles in regulating the hippocampal and cortical glutamatergic circuits that subserve affective regulation and cognitive function (41). Thus, changes in zinc homeostasis might compromise neuroplasticity and contribute to long-term neuropsychological and psychiatric decline (1,42). Although MDD is known to have an inflammatory component (43,44), it remains unclear whether inflammation plays a pathogenic role. Regardless, inflammation can reduce zinc status (45,46), and lower serum zinc has been associated with inflammatory markers in MDD (37,47–50). With regard to immune function, zinc is required for the development and maturation of T and B lymphocytes, and cellular immune abnormalities have been observed in MDD (37,47–50), particularly in relation to somatic symptoms (51). Finally, lower serum zinc has been associated with perturbations in fatty acid metabolism and serum lipids, which might affect brain function and vascular health (15,28,52). Indeed, lower serum zinc is associated with cardiovascular disease, which is a common MDD comorbidity (53,54).

Table 1. Characteristics of Included Studies and Patient Populations

Study	Clinical Setting	Number (Depressed, Control)	Percent Male (Depressed, Control)	Age (Depressed, Control)	Depression Severity	Criteria	Study Design	Antidepressant Use
Amani (26)	Community sample	23, 23	0, 0	20.7 ± 1.6, 20.2 ± 0.9	BDI = 47.2 ± 17.3	BDI > 19	CC	n/a
Crayton (women) (17)	Community sample	485, 28	0, 0	n/a , 45.7 ± 7.0	n/a	clinical diagnosis	CC	n/a
Crayton (men) (17)	Community sample	328, 26	100, 100	n/a, n/a	n/a	clinical diagnosis	CC	n/a
Grieger (10)	Community sample	28, 43	n/a	80.2 ± 10.6 (whole cohort)	GDS = 8.1 ± .0.4	GDS > 5	CS	n/a
Irmisch (15)	Psychiatric inpatient	88, 88	36, 36	45.1 ± 12.0, 46.0 ± 13.3	HAM-D = 20.5 ± 9.8, BDI = 19.9 ± 10.1	ICD-10 by CIDI	CC	75%
Maes (13)	Psychiatric inpatient	48, 32	n/a	49.6 ± 10.8, 43.8 ± 15.3	HAM-D = 19	SCID (DSM-III) (BDI < 9; Zung < 40)	CC	0%
Maes (27)	Psychiatric inpatient	36, 28	55.56, n/a	51.1 ± 13.7, 47.7 ± 14.2	HAM-D = 24.5 (q25 = 22.0; q75 = 27.0)	SCID (DSM-III-R semi-structured)	CC	0%
Maes (28)	Psychiatric inpatient	34, 14	52.94, 64.29	52.2 ± 13.6, 48.3 ± 15.2	HAM-D = 24.1 ± 4.1	SCID (DSM-III R)	CC	0%
McLoughlin (29)	Psychiatric inpatient	14, 14	21.43, 21.43	56.8, 56.2	HAM-D = 21 ± 2, BDI = 21 ± 6.3	Feighner's Research Diagnostic Criteria for Depression	CC	57%
Narang (16)	Community sample	35, 35	60, 60	n/a	n/a	HAMD ≥ 16; Feighner's Criteria for Depression	CC	0%
Nguyen (30)	Community sample	182, 187	0, 0	32.8 ± 9.3, 29.5 ± 9.2	n/a	CES-D ≥ 16	CS	n/a
Nowak (31)	Psychiatric inpatient	19, 16	36.84, 62.5	42.2 ± 10.6, 37 ± 9.1	HAM-D = 18.9 ± 5.3	SCID	CC	n/a
Salimi (32)	Psychiatric inpatient	144, 161	41.67, 42.24	38.53 ± 10.4, 35.37 ± 10.13	n/a	SCID	CC	0%
Salustri (33)	Psychiatric inpatient	13, 13	15.38, 15.38	54.2 ± 13.5, 55.9 ± 19.3	HAM-D, MADRS	SCID (DSM-IV)	CC	n/a
Siwek (14)	Both	60, 25	33.33, 36	45.9 ± 5.9, 43 ± 9.1	BDI = 35.9 ± 4.9	SCID (DSM-IV)	CC	0%
Stanley (34)	Both	21, 20	n/a	n/a	n/a	ICD 10	CC	0%
van Kempen (≥65) (11)	n/a	22, 17	27.27, 64.7	78 ± 7, 34 ± 7	n/a	SCID (DSM-III)	CC	n/a
van Kempen (<65) (11)	n/a	43, 17	26.2, 64.7	43 ± 12, 34 ± 7	n/a	SCID (DSM-III)	CC	n/a
Yang (12)	Psychiatric inpatient	33, 23	27.27, 39.13	42.12 ± 13.07, 38.35 ± 8.49	HAM-D ≥ 17	CCMD-3 and ICD-10	CC	0%

Mean ± SEM.

BDI, Beck Depression Inventory; CC, case-control; CCMD, Chinese Classification of Mental Disorders; CES-D, Center for Epidemiological Studies Depression scale; CIDI, Composite International Diagnostic Interview; CS, cross sectional; GDS, Geriatric Depression Scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; n/a, not available; SCID, Structured Clinical Interview.

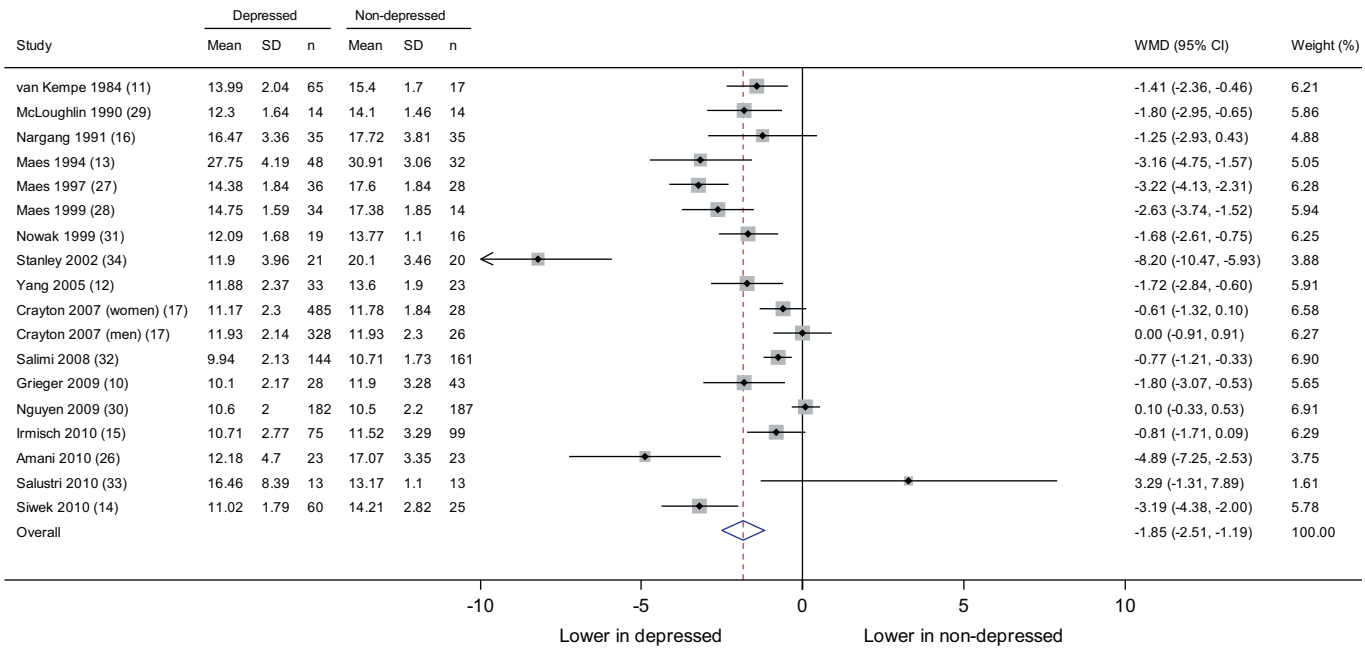

Figure 2. Peripheral blood zinc concentrations in depressed and control subjects (μmol/L). CI, confidence interval; WMD, weighted mean difference.

Blood zinc concentrations were chosen for this meta-analysis, because they are the most common measure used to assess zinc status. However, the sensitivity and specificity of serum concentrations to detect clinically relevant deficiencies are questionable (9), and the search for more sensitive biomarkers on the basis of cellular and molecular adaptations to zinc deficiency is on-going (55,56). In humans, several months of a zinc-deficient diet were required to appreciably change serum concentrations, although alterations in lymphocyte and platelet zinc concentrations and in other immunological parameters (e.g., T-cell number and serum concentrations of thymulin and interleukin-2) became apparent earlier (50). Serum zinc measurement might be confounded by regulatory mechanisms that preserve serum concentrations during shorter periods of dietary insufficiency; therefore, deficits in serum zinc might only indicate long-standing dietary deficiencies or deficiencies in these homeostatic mechanisms. Blood zinc concentrations are regulated by albumin, and zinc concentrations have been associated with albumin concentrations in depressed patients (32,57). Additionally, reciprocal relationships between concentrations of zinc and other micronutrients—particularly copper—have been observed, which might be clinically relevant (11,17,33,54); lower zinc in depression could be related to the status of other micronutrients (58).

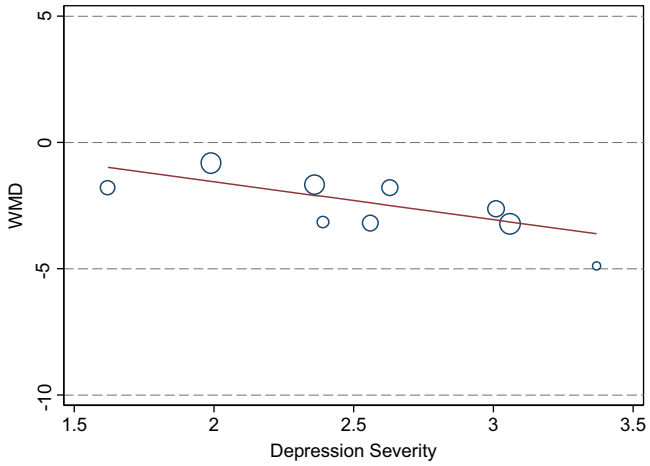

Figure 3. Depressive symptom severity in meta-regression analysis. Contribution of depressive symptom severity to the heterogeneity in effect sizes ($B = -1.503$, $t_8 = -2.82$, 95% confidence interval: −2.765 to −.242, $p = .007$) by inverse variance weighted meta-regression analysis. Symptom severity was compared across studies by normalizing the mean value to established cutoff values for the scales used in study reporting mean depression scores (see Statistical Analyses). WMD, weighted mean difference.

The extant literature on zinc and depression is largely limited to case-control and cross-sectional studies, which do not imply the direction of causation. Prospective cohort studies might be useful to establish whether lower zinc concentrations predict the future development of depression or vice versa. The possibility that depression might cause lower zinc concentrations warrants discussion, particularly because appetitive changes are a common component of MDD. One study of 48 MDD patients identified trends between lower zinc concentrations and weight loss and anorectic symptoms (13), suggesting that zinc deficiency could be related to dietary changes; however, zinc deficiency can also cause decreased appetite (59). Supplementation trials might be therefore most appropriate to establish the direction of causation. It should also be considered that common depression comorbidities such as alcohol dependence and cardiovascular disease might contribute to lower zinc status in depressed populations (53,54,60).

As a limitation, study quality and risk of bias were uneven among studies included in this meta-analysis. For example, not all studies reported demographic data sufficiently to be included in investigations of heterogeneity, the use of antidepressants and other concomitant medications were not consistently reported, and data on diet and alcohol use were often not reported. Few studies reported the proportions of patients below established cutoffs for zinc deficiency or estimated the difference in the prevalence of zinc deficiency between depressed and control

subjects. Significant heterogeneity was detected, necessitating the use of random effects models, which result in wider CIs; however, the effect estimates gleaned from subsets of studies stratified by study quality were statistically significant, and that from the high-quality subset was large and precise. Egger's test suggested potential publication bias but not in subgroups of studies defined by risk-of-bias items such as age- and gender-matching of control subjects and clinical setting or in the subset that used diagnostic criteria to differentiate patients from control subjects. Although the effect estimate from the latter studies was numerically smaller than that of the subset that relied on self-reported depressive symptoms inventories, the association remained highly significant.

In conclusion, the present meta-analytic results confirm that depression is associated with reduced concentrations of zinc in peripheral blood. The findings suggest the need to further investigate potential roles of zinc in the pathophysiology of depression, the potential utility of zinc and related biomarkers in monitoring MDD and its clinical sequelae, and potential benefits of zinc supplementation in MDD patients.

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