# Zinc in depression: From development to treatment: A comparative/ dose response metaanalysis of observational studies and randomized controlled trials

Yosaee, S., Clark, C. C. T., Keshtkaran, Z., Ashourpour, M., Keshani, P. & Soltani, S.

Author post-print (accepted) deposited by Coventry University's Repository

### Original citation & hyperlink:

Yosaee, S, Clark, CCT, Keshtkaran, Z, Ashourpour, M, Keshani, P & Soltani, S 2020, 'Zinc in depression: From development to treatment: A comparative/ dose response meta-analysis of observational studies and randomized controlled trials', General Hospital Psychiatry. https://dx.doi.org/10.1016/j.genhosppsych.2020.08.001

DOI 10.1016/j.genhosppsych.2020.08.001 ISSN 0163-8343

Publisher: Elsevier

NOTICE: this is the author's version of a work that was accepted for publication in General Hospital Psychiatry. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in General Hospital Psychiatry, (2020) DOI: 10.1016/j.genhosppsych.2020.08.001

© 2020, Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International <u>http://creativecommons.org/licenses/by-nc-nd/4.0/</u>

Copyright © and Moral Rights are retained by the author(s) and/ or other copyright owners. A copy can be downloaded for personal non-commercial research or study, without prior permission or charge. This item cannot be reproduced or quoted extensively from without first obtaining permission in writing from the copyright holder(s). The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the copyright holders.

This document is the author's post-print version, incorporating any revisions agreed during the peer-review process. Some differences between the published version and this version may remain and you are advised to consult the published version if you wish to cite from it.

Zinc in Depression: From development to treatment: A comparative/ dose response meta-1analysis of observational studies and randomized controlled trials2

3

### ABSTRACT

**Background:** A previous meta-analysis suggested that zinc status may be linked to depression 4 status. However, it remains unclear whether zinc status can predict the risk of depression 5 development, or whether the monotherapy of zinc is superior to the combination of zinc 6 supplementation and antidepressant medications in the treatment of depression. Therefore, this 7 meta-analysis aimed to clarify the impact of zinc status and supplementation on depression 8 development and status across all available evidence. 9

Methods: PubMed, EMBASE, Scopus, and ISI web of science were searched, up to 14 May 2020, 10
for relevant publications. Pooled relative risks (RRs) with 95% confidence intervals (CI) in 11
observational studies, and mean and standard deviation (SD) for the change in depression score in 12
RCTs were calculated using a random-effects model. 13

**Results:** The meta-analysis of RCTs indicated that zinc supplementation significantly lowered 14 depressive symptom scores of depressed patients [weighted mean difference (WMD = -4.15 point; 15 95% CI: -6.56, -1.75 point; P < 0.01)], and the improvement in depression status occurred only 16 when zinc supplementation was prescribed as a monotherapy. The cohort studies showed that the 17 highest level of zinc intake was associated with a 28% reduced risk of depression (RR: 0.66; 95% 18 CI: 0.50, 0.82; I<sup>2</sup> = 13.90). Dose-response analyses revealed a significant non-linear effect of 19 baseline mood status on depression score. 20

Conclusion: Current evidence from observational studies and RCT's supports the potential
benefits zinc to reduce the risk of, and alleviate, depression. However, further trials are needed to
confirm the beneficial effect of zinc as a monotherapy versus adjunctive therapies.
23

### **INTRODUCTION**

The monoamine hypothesis, accepted as the most common hypothesis with regard to the 29 pathophysiology of depression [1, 2], has led to the development of almost all currently used 30 antidepressant drugs [3], including selective serotonin reuptake inhibitors (SSRIs) or serotonin-31 norepinephrine reuptake inhibitors (SNRIs) [3, 4]. However, remission is achieved in only one-32 third of patients after treatment with SSRIs [3]. Antidepressants have latency of response [1, 5], 33 indeed, some evidence suggests that the monoamine hypothesis may be inadequate and emphasizes 34 the need for creating alternative, preventative and treatment, approaches to antidepressant 35 medication [1, 4]. Micronutrients currently represent the most prominent and valid alternate to 36 monoamine-based antidepressant medicine, as introduced in the "nutritional psychiatry 37 hypothesis" [6, 7]. 38

Zinc is a micronutrient to have received much attention, due to its' possible role in depression 39 [8]; for instance, zinc dysregulation in the hippocampus, amygdala, and the cerebral cortex is 40 purportedly linked to the pathophysiology of depression [9-13]. Furthermore, dysregulation of 41 brain zinc status is reported in many psychiatric and neurological disorders, such as 42 schizophrenia [14], mood disorders [15], Parkinson's [16], and Alzheimer's disease [16]. 43 Regulation of zinc levels within the brain may have a critical therapeutic role in neuropsychiatric 44 diseases [11]. Indeed, support for this hypothesis originates from studies' reporting that zinc 45 deprivation can induce depressive-like behavior, which can be effectively reversed by zinc 46 supplementation [17, 18]. Furthermore, it is conceivable that zinc could be used to enhance the 47 antidepressant effects of drugs belonging to the SSRI group [19, 20]. Considering this viewpoint, 48

2

25

26

27

a connection between zinc and depression is highly probable. Concordantly, a meta-analysis of 49 seventeen observational studies reported that serum zinc concentration was lower in depressive 50 patients, as compared to a healthy population, whilst the severity of depression status was related 51 to the degree of zinc deficiency [21]. A recent meta-analysis, by Li et al., reported an inverse 52 association between zinc status and risk of depression; however, this study exclusively 53 considered zinc intake [22]. Several meta-analyses have investigated the effect of zinc 54 supplementation on depression status, however, these studies mainly focused on the efficacy 55 adjunctive zinc therapy [23-25]. Notwithstanding the previous investigations, it is unclear 56 whether the monotherapy of zinc is superior to the combination of zinc supplementation and 57 antidepressant medications in depression, furthermore sources of heterogeneity are currently 58 unclear. Therefore, this meta-analysis sought to clarify the impact of zinc status and 59 supplementation on depression development and status across all available observational and 60 RCTs, and to conduct a dose-response analysis to investigate whether the effect of zinc 61 supplementation on depression symptoms had non-linear association. 62

### **Materials and Methods:**

The present systematic review and meta-analysis was conducted based on the Preferred Reporting 65 Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. We also followed 66 the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reporting 67 the meta-analysis of observational studies [27]. The review protocol was registered with the 68 Prospero International Prospective Register of Systematic Reviews (http://www.crd. 69 york.ac.uk/PROSPERO registration number CRD42018108150) 70

### Search strategy

71

63

64

PubMed, EMBASE, Scopus, and ISI web of science, were searched for relevant medical literature, 72 without language or publication date restriction, up to 14 May2020. The keywords used in our 73

search strategy were "zinc" and "depression". Further details about the search strategy in the
aforementioned databases are provided in **Supplementary Table 1**. Reference lists of previous
review papers that investigated the association between zinc and depression were also checked for
any additional studies that were not identified by the database searches. All titles and abstracts
were screened by two authors (SY and P Sh) to find eligible studies.

### Inclusion criteria

79

All publications with cross-sectional, cohort, case-cohort, and nested case-control designs, as well 80 as follow-ups of randomized controlled trials (RCTs) that described zinc-depression association, 81 were included. RCTs, as well as observational studies, were included if; 1) they were original 82 studies, 2) they reported depression score as outcome, 3) zinc was used as the intervention 83 approach (RCTs) or exposure/risk factor in observational studies, 4) the study was conducted in a 84 general adult population. If multiple studies were published on the same population, then the most 85 recent, with most complete reports, were included. RCT studies that addressed the effect of zinc 86 combined or compared with other vitamins and minerals were excluded. Studies were also 87 excluded if they were conducted in lactating/pregnant women. 88

### Data extraction

The following data from eligible studies were extracted: the name of first author, year of the 90 publication, country, study design, number of participants, depression score and tools, sex, length 91 of study or follow-up, type/dose of zinc used in the RCTs design and the method of zinc assessment 92 in observational studies, use of antidepressant medication, and list of adjusted variables in 93 observational studies. Data extraction and study selection were conducted independently by two 94 investigators (SY, MA). In instances of divergence, a third reviewer (SS) was consulted. 95

96 97

89

## Quality of evidence:

The Cochrane collaboration tool was used to assess the quality of the RCTs studies. This tool 98 categorizes the quality of studies into two levels: low quality, defined as a Cochrane collaboration 99

score lower than five points, and high quality defined as a score  $\geq 5$  [28]. A modified version of 100 the Newcastle Ottawa Scale (NOS), designed for nonrandomized studies, was used to quality 101 assessment of the eligible observational studies [29]. This scale has a range of 0 to 9, where studies 102 with scores equal 9 points represents the highest quality. 103

#### 104

### Statistical analysis

105

We conducted separate analyses for RCTs and observational studies, in order to address the 106 fundamental differences between these types of study designs. For RCTs studies, our outcome of 107 interest was the difference in pre to post-intervention changes in depression scores with control 108 groups. If changes were not reported, the mean and SD of changes from baseline to follow-up 109 were estimated for each intervention and control group using the calculated correlation 110 coefficient for studies that reported the baseline, after follow-up, and change values [r=0.67] [20, 111 30, 31]. We calculated the mean difference and its corresponding standard error (SE) as the 112 effect size to perform the meta-analysis, because the depression score values were reported in the 113 same scales (Beck questionnaire). The random-effects model was used to pool the data from 114 included studies when the extent of inconsistency ( $I^2$ ) was > 50 % [32]. Sensitivity analyses were 115 also conducted to evaluate the impact of individual studies on overall pooled estimates and 116 heterogeneity. We evaluated the potential sources of heterogeneity with the following subgroup 117 analyses: depression scale (Beck compared with Hamilton questioner), study duration (<12 118 weeks compared with  $\geq 12$  weeks), and adjunctive therapy (with or without anti-depressive agent 119 therapy). Moreover, a meta- regression analysis was conducted to check the effect of age, 120 baseline depression score, dose of zinc supplementation, and the study duration (as a continues 121 form) on predicting WMD of depression status. The potential non-linear effects of the age of 122 participants and baseline mood status on depression score was investigated using fractional 123 polynomial models for RCTs [33]. 124

For observational studies, the meta-analysis was performed by combining the multivariable-125 adjusted odds ratios (ORs) and their 95% confidence intervals (95% CIs) for comparing the 126 prevalence or the incidence of depression between groups with the highest and lowest zinc 127 status. Relative risks (RRs) were considered as ORs when used in the meta-analysis. The effect 128 size was pooled based on the random-effects model using the Der Simonian-Laird method, 129 which incorporated both within and between-study variability [34]. Statistical heterogeneity was 130 assessed using Cochran's Q test and I<sup>2</sup> statistic [35]. Publication bias was evaluated by Egger's 131 regression asymmetry test [36] and Begg's adjusted rank correlation test [37]. The meta-analysis 132 was performed with STATA software (version 13.0; Stata Corp), and P values less than 0.05 133 were considered statistically significant. 134

### RESULTS

Literature search and study characteristics. A total of thirteen observational studies (9 cross-136 sectional studies and four cohort studies) [38-49], and eight RCTs [19, 20, 30, 31, 50-53] met the 137 inclusion criteria for meta-analysis, from the 4245 articles initially retrieved from the electronic 138 search. The selection process of included studies is detailed in Supplementary Figure 1 and 139 140

135

### Supplementary Figure 2.

**RCT studies.** RCT studies were conducted between 2003 and 2018 [19, 20, 30, 31, 50-53]. These 141 studies provided data for 319 participants (intervention = 159, control= 160). Trial durations 142 ranged from 2 to 12 weeks; all studies conducted in both sexes. Three RCT studies investigated 143 the effect of zinc supplementation compared to placebo [51, 30, 31], whilst in five RCT studies, 144 the adjunctive effect of zinc versus antidepressant drugs was evaluated [50, 19, 20, 52, 53]. Most 145 RCTs were conducted in Iran [20, 30, 31, 50-52], and the remainder (n=2) were conducted in 146 Poland [19, 53]. The participants were depressed-only [19, 20, 31, 50-53] in most included studies, 147 except one study, which was conducted on a mixed population (depressed and non-depressed 148

subjects) [30]. The study by Sawada reported the effect of zinc supplementation compared to 149 multivitamins, thus, they were not included in the meta-analysis of RCTs [54]. Finally, eight RCT 150 studies were included in the final analysis (**Table 2**). The non-linear dose-response analysis failed 151 to detect any significant effect of participant's age on depression score (*P*-nonlinearity= 0.721) 152 (**Supplemental Figure 3**), although there was a non-linear trend between baseline mood status on 153 depression score in patients with mild to moderate depression (20-30 score) (**Supplemental Figure 4**).

**Observational studies:** Studies were published between 2012 and 2020, nine of which followed156a cross-sectional design [38, 41, 40, 42, 43, 45-47, 49]; two were carried out in the USA [45, 46],157five in Asia [38, 47, 40, 41, 49], one in Germany [43], and one in Australia [42]. From four158prospective cohort studies, three studies were conducted in Australia [39, 48], and one in Finland159[44]. The number of subjects and ages surveyed in the cross-sectional and prospective cohort160studies ranged from 297 to 14834 (age: <18-79 years), and from 1705 to 9738 (age: from <18 to</td>161 $\geq$ 70 year), respectively (**Table 1**).162

*Finding's from RCTs.* The seven meta-analyzed RCTs indicated a significantly greater 163 reduction in depression score with the zinc supplementation than with the control diets [weighted 164 mean difference (WMD = -4.15 point; 95% CI: -6.56, -1.75 point; P < 0.01)] (19, 20, 30, 31, 165 44-47), with substantial heterogeneity between studies ( $I^2 = 80.1\%$ ; P-heterogeneity 166 <0.001)(Figure 1). Subgroup analyses revealed that zinc supplementation significantly reduced 167 depression scores in depressive patients who received zinc supplementation in the absence of 168 anti-depressant medications (Table 3). The results of four models of meta-regression are 169 presented in Table 4. Age, dose of zinc supplementation, study duration, and baseline depression 170 score, in each study, were negatively associated with WMD for absolute change of depression 171 172 score.

The omission of each study, individually, from the meta-analysis did not alter the overall effects.173In addition, the Egger's linear regression tests (P=0.393) and Begg's test (P=0.368) did not174indicate evidence for potential publication bias (Supplementary Figure 5).175

Findings from prospective cohort studies.Four cohort studies (15852 Participants, 2243176incidence of depression) investigated the association between high versus low zinc intake and177risk of depression [39, 44, 48]. The highest level of zinc intake was associated with a 28%178reduced risk of depression (RR: 0.66; 95% CI: 0.50, 0.82;  $I^2 = 13.90\%$ ; P-heterogeneity= 0.323)179(Figure 2).180

*Findings from cross-sectional studies.* Overall, combining effect sizes from 9 studies [38, 41,18140, 42, 43, 45-47, 49], that included 27296 participants and 3646 cases of depressive patients,182revealed that high zinc status (a combination of dietary zinc and serum zinc concentration) was183inversely associated with risk of depression (RR: 0.61; 95% CI: 0.51, 0.70) (**Figure 3**), with a184low between-study heterogeneity (I<sup>2</sup> = 0.0 %, P = 0.420).185

### Study quality

Based on the Cochrane tools used, the seven RCTs presented high methodologic quality [19, 20, 187
52, 51, 53, 30, 31] (Supplementary Table 2). All cohort studies were recorded to have good 188
quality [39, 44, 48] (Supplementary Table 3). In the cross-sectional studies, four studies were 189
good [42, 43, 45, 41], however the remaining studies were scored as moderate to low quality [38, 190
46, 47, 40, 49] (Supplementary Table 4).

192

### **Discussion:**

The present systematic review and meta-analysis of observational and RCTs studies sought to 194 explicate the impact of zinc status and supplementation on depression development and treatment. 195 First, our meta-analysis of cross-sectional studies revealed that inadequate zinc status (a 196 combination of dietary zinc and serum zinc concentration) is prevalent among depressed patients. 197 Second, we found that the highest level of zinc intake was associated with a 28% reduced risk of 198 depression in the analysis of prospective cohort studies. Third, the result of the RCTs analysis 199 confirmed the findings from observational studies regarding lower levels of zinc in depressed 200 patients, and highlighted that zinc supplementation can significantly reduce depression score in 201 depressive patients, when supplementing with zinc, in the absence of anti-depressant medications 202 (monotherapy). Finally, this meta-analysis showed zinc supplementation had a beneficial effect on 203 depression symptoms in patients with a depression score of 20-30 (mild to moderate depression). 204

Findings from the present updated meta-analysis are in line with the previous meta-analysis that 205 shows an inverse association between zinc status and risk of depression [22, 21], the potential to 206 alleviate depression symptoms following zinc supplementation, and, adding to previous studies, 207 that only zinc monotherapy significantly affected depression score. Furthermore, based on the 208 current meta-analysis, the largest antidepressant effect of zinc supplementation was reported in 209 mild to moderately depressed subjects. 210

Micronutrient deficiencies are reported to be more frequent in depressed patients compared to 211 healthy individuals [45, 55] . Indeed, deficiencies in key vitamins and minerals can interrupt the 212 brain functioning and increase levels of stress. Zinc is one of the most important micronutrients, 213 and plays a major role in the ability to regulate biological and psychological factors, and its 214 inextricable association with depression has received much attention in field of nutrition and 215 psychology in contemporary research. Zinc deficiency is known to increase Reactive Oxygen 216 Species (ROS) and oxidative stress, and both are involved in the physiopathology of depression 217 [55, 56, 15]. Second, it is accepted that synaptic zinc is an N-methyl-D-aspartate (NMDA) receptor 218 antagonist [57, 58]; indeed, NMDA antagonists were found to be therapeutically targeted in studies 219 of depression treatment [55, 59]. Further, according to animal-based investigations, blockade of 220 NMDA receptors can eliminate the beneficial effects of zinc on depressive related symptoms, 221 suggesting that NMDA receptors are a mediator of the antidepressant properties of zinc [60]. 222 Furthermore, the effect on hormonal regulation, cortisol, cellular immune response [61], 223 neurogenesis, neural plasticity, and expression of hippocampal and cortical brain-derived 224 neurotrophic factor (BDNF) [30, 55] are considered as additive explanations for the beneficial 225 effect of zinc in patients with depression. 226

In the meta-regression models; age, dose of zinc supplementation, study duration, and baseline 227 depression score made significant contributions to the change of depression. Indeed, higher doses 228 of supplementation, longer intervention duration , and older adults with severe depression, 229 respectively, were associated with an enhanced effect of zinc supplementation for decreasing 230 depression score. However, due to the limited available evidence, these findings should be 231 interpreted with caution 232

This meta-analysis study included several lines of evidence; cross-sectional, prospective cohort, 233 and intervention studies; which strongly support the zinc-depression relationship. While original 234 [50, 19, 20] intervention studies have reported zinc may be efficacious as an adjunctive therapy 235 for depression, our study revealed that mood-enhancing properties of zinc supplementation can be 236 observed in depressed patients who supplement with zinc in the absence of anti-depressant 237 medications (zinc monotherapy). This is important, because, while prescribers continue 238 antidepressant therapy, early antidepressant discontinuation is widespread in the community of 239 depressed patients [62]; in addition, relapses are prevalent and costly to healthcare systems [62, 240 63]. 241 A strength of the present meta-analysis is that it was the first to examine the effect of zinc 242 monotherapy compared to placebo in depressed patients in RCTs. In addition, the dose-response 243 relationship between zinc supplementation on depression status was in investigated, albeit a 244 limited number of studies were eligible for analysis. However, in addition to the strengths and 245 novelty of the present meta-analysis, there are some limitations that should be considered. 246 Regarding the cohort studies, most included cohort studies in this meta-analysis had adjusted for 247 potential confounders, including age, gender, socioeconomic status, BMI, physical activity, 248 smoking status, but only two studies had adjusted for other micronutrients, including vitamin B 249 family and vitamin D intake, as a confounder of risk of depression development [43, 47]. The 250 different confounder adjustments among studies may lead to bias of the pooled results. Dietary 251 zinc intake has been the main method for zinc status evaluation in observational studies, which is 252 prone to measurement errors in zinc status assessment. Inconsistent criteria were used to 253 diagnose depression among the observational studies included in the meta-analysis, which 254 conceivably could have affected the strength of the association between zinc status and 255 depression status. 256

Regarding RCTs, we are not aware of an intervention study to have examined the effect of zinc 257 supplementation on healthy subjects, and our results may, therefore, not be generalizable to a 258 healthy population. Furthermore, in the present analysis, the number of eligible studies was small; 259 however, comparatively, the previous meta-analysis in this field was conducted in fewer trials. 260 The Beck depression scale used to determine depression status in all included studies; however, 261 various thresholds in Beck scale criteria to categorize depression were applied in the RCTs; hence, 262 it was difficult to distinguish the true effect of zinc supplementation on the severity of depression. 263 All of the eligible RCTs followed their participants for less than six months, therefore, whether 264 the effect of zinc supplementation persists for a longer period of time remains unknown, and 265 therein represents a viable avenue for further research. An important limitation present in most of 266

the included studies was that they were conducted in a relatively low range of geographical	267
locations (3 from 4 cohort studies established in Australia [39, 48], and 6 from 8 RCTs conducted	268
in Iran[20, 52, 51, 30, 31]), thus, the association between zinc status and risk of depression may	269
not be congruent in different populations, and clearly warrants further investigation. Although we	270
conducted several subgroup analyses, we were unable to adequately detect the sources of	271
heterogeneity.	272

In conclusion, our findings advocate the preventative and therapeutic effect of zinc, compared to 273 traditional antidepressant therapy, as a cost-efficient, efficacious, alternative approach. Future 274 studies are needed to elucidate the effects of zinc intake on the depression-related symptoms in 275 healthy individuals and in wider geographical locations. 276

### References:

281	
282	

	202
1. Boku S, Nakagawa S, Toda H, Hishimoto A. Neural basis of major depressive disorder: beyond	283
monoamine hypothesis. Psychiatry and clinical neurosciences. 2018;72(1):3-12.	284
2. Hirschfeld R. History and evolution of the monoamine hypothesis of depression. The Journal of clinical	285
psychiatry. 2000.	286
3. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L et al. Evaluation of outcomes	287
with citalopram for depression using measurement-based care in STAR* D: implications for clinical	288
practice. American journal of Psychiatry. 2006;163(1):28-40.	289
4. Doboszewska U, Wlaź P, Nowak G, Radziwoń-Zaleska M, Cui R, Młyniec K. Zinc in the monoaminergic	290
theory of depression: its relationship to neural plasticity. Neural plasticity. 2017;2017.	291
5. Racagni G, Popoli M. Cellular and molecular mechanisms in the long-term action of antidepressants.	292
Dialogues in clinical neuroscience. 2008;10(4):385.	293
6. Logan AC, Jacka FN. Nutritional psychiatry research: an emerging discipline and its intersection with	294
global urbanization, environmental challenges and the evolutionary mismatch. Journal of physiological	295
anthropology. 2014;33(1):22.	296
7. Martínez-Cengotitabengoa M, González-Pinto A. Nutritional supplements in depressive disorders.	297
Actas Esp Psiquiatr. 2017;45(1):8-15.	298
8. Szewczyk B. Zinc homeostasis and neurodegenerative disorders. Frontiers in aging neuroscience.	299
2013;5:33.	300
9. Ebadi M. [43] Metallothioneins and other zinc-binding proteins in brain. Methods in enzymology.	301
Elsevier; 1991. p. 363-87.	302
10. Frederickson CJ. Neurobiology of zinc and zinc-containing neurons. International review of	303
neurobiology. Elsevier; 1989. p. 145-238.	304
11. M Grabrucker A, Rowan M, C Garner C. Brain-delivery of zinc-ions as potential treatment for	305
neurological diseases: mini review. Drug delivery letters. 2011;1(1):13-23.	306
12. Maske H. Über den topochemischen Nachweis von Zink im Ammonshorn verschiedener Säugetiere.	307
Naturwissenschaften. 1955;42(14):424	308
13. Mocchegiani E, Bertoni-Freddari C, Marcellini F, Malavolta M. Brain, aging and neurodegeneration:	309
role of zinc ion availability. Progress in neurobiology. 2005;75(6):367-90.	310
14. Rahman MA, Azad MAK, Hossain MI, Qusar MS, Bari W, Begum F et al. Zinc, manganese, calcium,	311
copper, and cadmium level in scalp hair samples of schizophrenic patients. Biological trace element	312
research. 2009;127(2):102-8.	313
15. Cope EC, Levenson CW. Role of zinc in the development and treatment of mood disorders. Current	314
Opinion in Clinical Nutrition & Metabolic Care. 2010;13(6):685-9.	315
16. Brewer GJ, Kanzer SH, Zimmerman EA, Molho ES, Celmins DF, Heckman SM et al. Subclinical zinc	316 317
deficiency in Alzheimer's disease and Parkinson's disease. American Journal of Alzheimer's Disease & Other Dementias <sup>®</sup> . 2010;25(7):572-5.	317 318
	318 319
17. Młyniec K, Davies CL, Budziszewska B, Opoka W, Reczyński W, Sowa-Kućma M et al. Time course of zinc deprivation-induced alterations of mice behavior in the forced swim test. Pharmacological Reports.	320
2012;64(3):567-75.	320
18. Młyniec K, Nowak G. Zinc deficiency induces behavioral alterations in the tail suspension test in	321
mice. Effect of antidepressants. Pharmacological Reports. 2012;64(2):249-55.	323
19. Nowak G, Siwek M, Dudek D, Ziêba A, Pilc A. Effect of zinc supplementation on antidepressant	323
therapy in unipolar depression: a preliminary placebo-controlled study. Polish journal of pharmacology.	324
2003;55(6):1143-8.	325
2003,55(0).1143-8. 20. Ranjbar E, Kasaei MS, Mohammad-Shirazi M, Nasrollahzadeh J, Rashidkhani B, Shams J et al. Effects	320
of zinc supplementation in patients with major depression: a randomized clinical trial. Iranian journal of	328
psychiatry. 2013;8(2):73.	329
	525

21. Swardfager W, Herrmann N, Mazereeuw G, Goldberger K, Harimoto T, Lanctôt KL. Zinc in depression: a meta-analysis. Biological psychiatry. 2013;74(12):872-8.	330 331
22. Li Z, Li B, Song X, Zhang D. Dietary zinc and iron intake and risk of depression: A meta-analysis. Psychiatry research. 2017;251:41-7.	332 333
23. Lai J, Moxey A, Nowak G, Vashum K, Bailey K, McEvoy M. The efficacy of zinc supplementation in depression: systematic review of randomised controlled trials. Journal of affective disorders. 2012;136(1-2):e31-e9.	334 335 336
24. Sarris J, Murphy J, Mischoulon D, Papakostas GI, Fava M, Berk M et al. Adjunctive nutraceuticals for	337
depression: a systematic review and meta-analyses. American Journal of Psychiatry. 2016;173(6):575-87. 25. Schefft C, Kilarski LL, Bschor T, Koehler S. Efficacy of adding nutritional supplements in unipolar	338 339
depression: a systematic review and meta-analysis. European Neuropsychopharmacology. 2017;27(11):1090-109.	340 341
26. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP et al. The PRISMA statement	342
for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009;6(7):e1000100.	343 344
27. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al. Meta-analysis of	345
observational studies in epidemiology: a proposal for reporting. Jama. 2000;283(15):2008-12.	346
28. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2011.	347 348
29. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS)	349
for assessing the quality if nonrandomized studies in meta-analyses. 2009. Epub Available from: URL:	350
http://www ohri ca/programs/clinical_epidemiology/oxford htm [cited 2009 Oct 19]. 2016.	351
30. Solati Z, Jazayeri S, Tehrani-Doost M, Mahmoodianfard S, Gohari MR. Zinc monotherapy increases	352
serum brain-derived neurotrophic factor (BDNF) levels and decreases depressive symptoms in	353
overweight or obese subjects: a double-blind, randomized, placebo-controlled trial. Nutritional	354
neuroscience. 2015;18(4):162-8.	355
31. Yosaee S, Soltani S, Esteghamati A, Motevalian A, Tehrani-Doost M, Clark CC et al. Effects of zinc,	356
vitamin D and their co-supplementation on mood, serum cortisol, and brain-derived neurotrophic factor	357
in patients with obesity and mild to moderate depressive symptoms: A 12-week, 2× 2 factorial design,	358
double-blind, randomized, placebo-controlled trial phase II. Nutrition. 2019:110601.	359
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj.	360
2003;327(7414):557-60.	361
33. Fan J, Gijbels I. Local polynomial modelling and its applications: monographs on statistics and applied	362
probability 66. CRC Press; 1996.	363
34. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.	364
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine.	365
2002;21(11):1539-58.	366
36. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629-34.	367 368
37. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J et al. Recommendations for examining	369
and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj. 2011;343:d4002.	370 371
38. Anbari-Nogyni Z, Bidaki R, Madadizadeh F, Sangsefidi ZS, Fallahzadeh H, Karimi-Nazari E et al.	372
Relationship of zinc status with depression and anxiety among elderly population. Clinical nutrition	373
ESPEN. 2020;37:233-9. doi:10.1016/j.clnesp.2020.02.008.	374
39. Das A, Cumming RG, Naganathan V, Ribeiro RV, Le Couteur DG, Handelsman DJ et al. The association	375
between antioxidant intake, dietary pattern and depressive symptoms in older Australian men: the	376
Concord Health and Ageing in Men Project. European journal of nutrition. 2020. doi:10.1007/s00394-020-02255-8.	377 378

Intake is Associated with Depression and Anxiety Symptoms in the Japanese Working Population.       382         Findings from the Eating Habit and Well-Being Study. Nutrients. 2019;11(4). doi:10.3390/nut1040847.       383         Hun Yuguyen T, Miyagi S, Tsujiguchi H, Kambayashi Y, Hara A, Nakamura H et al. Association       382         Men: Findings from Shika Study. Nutrients. 2019;11(2). doi:10.3390/nut10020389.       384         Jacka FN, Maes M, Pasco JA, Williams LJ, Berk M. Nutrient intakes and the common mental disorders       383         43. Jung A, Spina D, Steinhagen-Thiessen E, Demuth I, Norman K. Zinc deficiency is associated with       383         depressive symptoms—results from the Berlin Aging Study II. Journals of Gerontology Series A:       388         Biomedical Sciences. 2016;72(8):1149-54.       383         44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake       390         and the risk of depression in middle-aged men: a 20-year prospective follow-up study. Journal of       391         45. U2, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes       392         46. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression symptoms among women, but not men, in a population-based epidemiological survey. Journal of 396       393         47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary rinc is associated with a 400       394         48. Maserejian NN, H	40. Nakamura M, Miura A, Nagahata T, Shibata Y, Okada E, Ojima T. Low Zinc, Copper, and Manganese	379
<ul> <li>Findings from the Eating Habit and Well-Being Study, Nutrients. 2019;11(4). doi:10.390/nu11040847.</li> <li>Thi Thu Nguyen T, Miyagi S, Tsuijiguchi H, Kambayashi Y, Hara A, Nakamura H et al. Association</li> <li>Jaka FM, Maes M, Pasco JA, Williams LJ, Berk M, Nutrient in takes and the common mental disorders</li> <li>Jaka FM, Maes M, Pasco JA, Williams LJ, Berk M, Nutrient in takes and the common mental disorders</li> <li>Jaka FM, Maes M, Pasco JA, Williams LJ, Berk M, Nutrient in takes and the common mental disorders</li> <li>Jaka FM, Maes M, Pasco JA, Williams LJ, Berk M, Nutrient in takes and the common mental disorders</li> <li>Jaka FM, Maes M, Pasco JA, Williams LJ, Berk M, Nutrient in takes and the common mental disorders</li> <li>Jaka FM, Maes M, Pasco JA, Williams LJ, Berk M, Nutrient in takes and the common mental disorders</li> <li>Jaka FM, Ka Maes M, Pasco JA, Sako JA, Jaka JA, J</li></ul>		
41. Thi Thu Nguyen T, Miyagi S, Tsuijguchi H, Kambayashi Y, Hara A, Nakamura H et al. Association       383         between Lower Intake of Minerals and Depressive Symptoms among Elderly Japanese Women but Not       383         Men: Findings from Shika Study, Nutrients. 2019;11(2). doi:10.3390/nu11020389.       384         42. Jacka FN, Maes M, Pasco JA, Williams LJ, Berk M. Nutrient Intakes and the common mental disorders       388         43. Jung A, Spira D, Steinhagen-Thiessen E, Demuth I, Norman K. Zinc deficiency is associated with       387         depressive symptoms—results from the Berlin Aging Study II. Journals of Gerontology Series A:       388         Biomedical Sciences. 2006;72(8):1149-54.       388         44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake       392         and the risk of depression in middle-aged men: a 20-year prospective follow-up study. Journal of       393         affective disorders. 2013;150(2):682-5.       394         45. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes       393         affective disorders. 2012;136(3):781-8.       394         47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in       396         48. Vastami S, Dietary intake of rinc was inversely associated with depression. Biological trace       404         49. Yan Y, Arazami S. Dietary intake of rinc was inversely associated with depression.		
between Lower Intake of Minerals and Depressive Symptoms among Elderly Japanese Women but Not         383           Men: Findings from Shika Study, Nutrients. 2019;11(2). doi:10.3390/nu11020389.         383           42. Jacka FN, Maes M, Pascudy, Nutrients. 2019;11(2). doi:10.3390/nu11020389.         384           42. Jacka FN, Maes M, Pascudy, Nutrients. 2012;141(1):79-85.         386           Biomedical Sciences. and Medical Sciences. 2016;72(8):1149-54.         384           44. Lehto SM, Ruusune A, Tolmunen T, Youtilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake and the risk of depression and medical Sciences. 2016;72(8):1149-54.         393           45. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes 393         394           46. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression in the US adults. Journal of affective disorders. 2012;228:68-74.         394           46. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression symptoms among women, but not men, in a population-based epidemiological survey. Journal of affective disorders. 2012;136(3):781-8.         397           47. Miki T, Koch T, Egucchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 2012;136(3):686-90.         400           48. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian coho		
Men: Findings from Shika Study, Nutrients. 2019;11(2). doi:10.3390/nu11020389.       384         42. Jacka FN, Maes M, Pasco JA, Williams LJ, Berk M. Nutrient intakes and the common mental disorders       386         42. Jacka FN, Maes M, Pasco JA, Williams LJ, Berk M. Nutrient intakes and the common mental disorders       386         43. Jung A, Spira D, Steinhagen-Thiessen E, Demuth I, Norman K. Zinc deficiency is associated with       387         depressive symptoms—results from the Berlin Aging Study II. Journals of Gerontology Series A:       386         Biomedical Sciences and Medical Sciences. 2016;72(8):1149-54.       388         44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake and the risk of depression in middle-aged men: a 20-year prospective follow-up study. Journal of affective disorders. 2013;150(2):682-5.       392         45. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes       395         947. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in       392         947. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 2012;31(5):68-90.       400         948. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 2012;31(5):68-90.       400 <t< td=""><td></td><td></td></t<>		
<ul> <li>42. Jacka FN, Maes M, Pasco JA, Williams LJ, Berk M. Nutrient intakes and the common mental disorders</li> <li>43. Jurq A, Spira D, Steinhagen-Thiessen E, Demut H, Norman K. Zinc deficiency is associated with</li> <li>43. Jurg A, Spira D, Steinhagen-Thiessen E, Demut H, Norman K. Zinc deficiency is associated with</li> <li>44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake</li> <li>44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake</li> <li>44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake</li> <li>44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake</li> <li>45. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes</li> <li>45. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes</li> <li>46. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression</li> <li>47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in</li> <li>47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary zinc is associated with a</li> <li>49. Yary T, Azarami S. Dietary intake of zinc was inversely associated with depression. Biological trace</li> <li>40. Yary T, Azarami S. Dietary intake of zinc was inversely associated with depression. Biological trace</li> <li>40. Yary T, Azarami S. Dietary intake of zinc was inversely associated with depression. Biological trace</li> <li>40. Yary T, Azarami S. Dietary intake of zinc was inversely associated with depression. Biological trace</li> <li>40. Yary T, Azarami S. Dietary intake of zinc was inversely associated with depression. Biological trace</li> <li>40. Yary T, Azarami S. Dietary intake of zinc was inversely associate</li></ul>		
in women. Journal of affective disorders. 2012;141(1):79-85. 386 43. Jung A, Spira D, Steinhagen-Thiessen E, Demuth I, Norman K. Zinc deficiency is associated with 387 44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake 396 397 398 44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake 399 307 308 309 316 316 317 317 318 319 319 319 310 319 310 310 310 310 310 310 310 310		
<ul> <li>43. Jung A, Spira D, Steinhagen-Thiessen E, Demuth I, Norman K. Zinc deficiency is associated with</li> <li>45. Jung A, Spira D, Steinhagen-Thiessen E, Demuth I, Norman K. Zinc deficiency is associated with</li> <li>46. Description of the Berlin Aging Study II. Journals of Gerontology Series A:</li> <li>87. Biomedical Sciences and Medical Sciences. 2016;72(3):1149-54.</li> <li>88. Stonedical Sciences. 2016;72(3):1149-54.</li> <li>89. At. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake</li> <li>and the risk of depression in middle-aged men: a 20-year prospective follow-up study. Journal of</li> <li>89. At. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake</li> <li>40. Mascrejan NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression</li> <li>89. Symptoms among women, but not men, in a population-based epidemiological survey. Journal of</li> <li>89. Samptoms in Japanese employees: the Furukawa Nutrition and Health Study.</li> <li>80. Natering Y, McKiroy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a</li> <li>80. Natum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a</li> <li>80. Natum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a</li> <li>80. Natum KP, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace</li> <li>80. Natura F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving</li> <li>80. Natura T, Aszami S, Dietary intake of zinc was inversely associated with depression applementation on efficacy of antidepression. Nutritional neuroscience. 2014;17(2):65-71.</li> <li>81. Salari S, Khomand P, Arasteh M, Yousefazamai B, Hassanzadeh K. Zinc sulphate: a reasonable choice</li> <li>82. Ranjibar E, Shams J, Sabetkasaei M, M-</li></ul>		
depressive symptoms — results from the Berlin Aging Study II. Journals of Gerontology Series A:388Biomedical Sciences and Medical Sciences. 2016;72(8):1149-54.38644. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake391affective disorders. 2013;150(2):682-5.39245. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes393with depression in the US adults. Journal of affective disorders. 2018;228:68-74.39446. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression395symptoms among women, but not men, in a population-based epidemiological survey. Journal of396affective disorders. 2012;136(3):781-8.39747. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in395vantition. 2015;31(5):686-90.40048. vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a400lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.4022013;165:249-57.40249. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace404element research. 2012;145(3):286-90.40550. Nazzinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving40540. depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan40515. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a re		
Biomedical Sciences and Medical Sciences. 2016;72(8):1149-54.       385         44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake       390         and the risk of depression in middle-aged men: a 20-year prospective follow-up study. Journal of       391         affective disorders. 2013;150(2):682-5.       392         45. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes       393         46. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression in the US adults. Journal of affective disorders. 2012;136(3):781-8.       397         47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in       392         relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study.       307         Nutrition. 2015;31(5):686-90.       400         48. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a       401         lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.       402         oly:14;61:249-57.       402         49. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace       404         element research. 2012;145(3):266-90.       402         50. Nazarinasab M, Behrouzina F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improvin		
<ul> <li>44. Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen T-P, Kauhanen J. Dietary zinc intake</li> <li>and the risk of depression in middle-aged men: a 20-year prospective follow-up study. Journal of</li> <li>affective disorders. 2013;150(2):682-5.</li> <li>45. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes</li> <li>with depression in the US adults. Journal of affective disorders. 2018;228:68-74.</li> <li>46. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression</li> <li>symptoms among women, but not men, in a population-based epidemiological survey. Journal of</li> <li>affective disorders. 2012;136(3):781-8.</li> <li>47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in</li> <li>relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study.</li> <li>Nutrition. 2015;31(5):686-90.</li> <li>40. Washum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a</li> <li>40. Hower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.</li> <li>2014;166:249-57.</li> <li>40. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving</li> <li>depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan</li> <li>Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;56(3):66-61.</li> <li>51. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice</li> <li>for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):66-9.</li> <li>52. Ranjbar E, Shams J, Sabetkasael M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc</li> <li>supplementation on</li></ul>		
and the risk of depression in middle-aged men: a 20-year prospective follow-up study. Journal of affective disorders. 2013;150(2):682-5.39145. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes with depression in the US adults. Journal of affective disorders. 2018;228:68-74.39446. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression symptoms among women, but not men, in a population-based epidemiological survey. Journal of affective disorders. 2012;136(3):781-8.39747. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study. Nutrition. 2015;31(5):686-90.40048. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 2014;166:249-57.40049. Yary T, Azami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90.40050. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving dof depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40151. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice of depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi		
affective disorders. 2013;150(2):682-5.39245. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes393with depression in the US adults. Journal of affective disorders. 2018;228:68-74.39446. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression395symptoms among women, but not men, in a population-based epidemiological survey. Journal of396affective disorders. 2012;136(3):781-8.3977. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in398relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study.390Nutrition. 2015;31(5):686-90.40048. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a401lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.4022014;166:249-57.40349. Yary T, Azazmi S. Dietary intake of zinc was inversely associated with depression. Biological trace404element research. 2012;145(3):286-90.40550. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving406Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40551. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice404for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo-41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et		
45. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes393with depression in the US adults. Journal of affective disorders. 2018;228:68-74.39446. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression395symptoms among women, but not men, in a population-based epidemiological survey. Journal of396affective disorders. 2012;136(3):781-8.39747. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in396relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study.392Nutrition. 2015;31(5):686-90.40048. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a400lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.4022014;166:249-57.40349. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace404element research. 2012;145(3):286-90.40650. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving406depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan407Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40551. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice406controlled clinical trial. Pharmacological Reports. 2015;67(3):666-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, R		
<ul> <li>with depression in the US adults. Journal of affective disorders. 2018;228:68-74.</li> <li>46. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression symptoms among women, but not men, in a population-based epidemiological survey. Journal of affective disorders. 2012;136(3):781-8.</li> <li>47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study.</li> <li>Nutrition. 2015;31(5):686-90.</li> <li>48. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.</li> <li>402 49. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90.</li> <li>40. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan 407</li> <li>Hospital in Ahvaz, Iran. Minerva Psichatrica. 2017;58(3):156-61.</li> <li>51. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.</li> <li>52. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc 412</li> <li>53. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal of affective disorders. 2009;118(1-3):187-95.</li> <li>54. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.</li> <li>55. Wang J, Um P, Dickerman BA,</li></ul>		
<ul> <li>46. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression symptoms among women, but not men, in a population-based epidemiological survey. Journal of affective disorders. 2012;136(3):781-8.</li> <li>47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in grelation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study.</li> <li>48. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.</li> <li>402</li> <li>49. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90.</li> <li>405</li> <li>50. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan</li> <li>407</li> <li>408</li> <li>409</li> <li>409</li> <li>409</li> <li>400</li> <li>400</li> <li>400</li> <li>401</li> <li>402</li> <li>402</li> <li>402</li> <li>403</li> <li>403</li> <li>404</li> <li>404</li> <li>404</li> <li>405</li> <li>405</li> <li>406</li> <li>50. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.</li> <li>410</li> <li>51. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice difficacy of mitparmetation on efficacy of antidepression. Nutritional neuroscience. 2014;17(2):65-71.</li> <li>414</li> <li>415</li> <li>416</li> <li>417</li> <li>51. Swada T, Yokoi K. Ef</li></ul>		
symptoms among women, but not men, in a population-based epidemiological survey. Journal of affective disorders. 2012;136(3):781-8. 397 47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study. 400 48. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 402 49. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90. 405 50. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan 405 for depression management in patients treated with selective serotonin reuptake inhibitors in Golestan 406 for depression management in patients with multiple sclerosis: a randomized. 407 52. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc 408 supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived 417 supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived 418 sefficaty of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal 417 54. Sawada T, Yokoi K. Effect of zinc supplementation nuo ds states in young women: a pilot study. 417 55. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the 420 evidence, potential mechanisms and implications. Nutritens. 2018;10(5):584. 421 56. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal 422 2008;1237:52-61. 423 57. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA 425 systems as targets for novel antide		
affective disorders. 2012;136(3):781-8.39747. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in signed to be pressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study. Nutrition. 2015;31(5):686-90.40048. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 2014;166:249-57.40049. Yary T, Azzami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90.40050. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression sin patients treated with selective serotonin reuptake inhibitors in Golestan Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61. 40040051. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9. 41141152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc aupplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived 41241253. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments affective disorders. 2009;118(1-3):187-95.41254. Sawada T, Yoko K. Effect of zinc supplementation on mood states in young women: a pilot study. Luropean journal of clinical nutrition. 2010;64(3):331.41255. Wang J, Um P, Dickerman BA, Liu		
<ul> <li>47. Miki T, Kochi T, Eguchi M, Kuwahara K, Tsuruoka H, Kurotani K et al. Dietary intake of minerals in relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study.</li> <li>Nutrition. 2015;31(5):686-90.</li> <li>40. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.</li> <li>2014;166:249-57.</li> <li>402</li> <li>49. Yay T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90.</li> <li>406</li> <li>407</li> <li>408 element research. 2012;145(3):286-90.</li> <li>50. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan</li> <li>407</li> <li>405</li> <li>51. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.</li> <li>411</li> <li>52. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc supplementation on efficacy of antidepression. Nutritional neuroscience. 2014;17(2):65-71.</li> <li>412</li> <li>53. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments efficaty of zinc supplementation on mood states in young women: a pilot study.</li> <li>415</li> <li>54. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.</li> <li>415</li> <li>416</li> <li>417</li> <li>54. Sawada K, Kitigha A, Popik P et al. Sinc deficiency impairs neuronal proteins and implications. Nutritions. 2010;(5):584.</li> <li>416</li> <li>417</li> <li>55. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium,</li></ul>		
relation to depressive symptoms in Japanese employees: the Furukawa Nutrition and Health Study. Nutrition. 2015;31(5):686-90. 40. 40. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 40. 40. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90. 50. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving 40. 40. Hopstral in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61. 51. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9. 52. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc supplementation on efficacy of antidepression. Nutritional neuroscience. 2014;17(2):65-71. 53. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal of affective disorders. 2009;118(1-3):187-95. 54. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study. European journal of clinical nutrition. 2010;64(3):331. 55. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584. 56. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal 208;1237:52-61. 57. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA 202;7(S1):571. 58. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscienc		
Nutrition. 2015;31(5):686-90.40048. Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 2014;166:249-57.40049. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90.40050. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40051. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived 413 neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments efficacy of inipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal of affective disorders. 2009;118(1-3):187-95.41654. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.41664. Sortical antrition. 2010;64(3):331.42055. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of		
<ul> <li>Vashum KP, McEvoy M, Milton AH, McElduff P, Hure A, Byles J et al. Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders. 2014;166:249-57.</li> <li>Vagy T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace element research. 2012;145(3):286-90.</li> <li>So. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan 407</li> <li>Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.</li> <li>So. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- 410</li> <li>controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.</li> <li>Sz. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc supplementation on efficacy of antidepression. Nutritional neuroscience. 2014;17(2):65-71.</li> <li>Si Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal of affective disorders. 2009;118(1-3):187-95.</li> <li>Swada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.</li> <li>European journal of clinical nutrition. 2010;64(3):331.</li> <li>So. Ward J, Wan KA, Karma G, Levenson CW. Zinc deficiency impairs neuronal precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.</li> <li>2008;1237:52-61.</li> <li>Sr. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA 425</li> <li>Systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.</li> <li>2002;7(51):571.</li> <li>S.</li></ul>		
lower incidence of depression: findings from two Australian cohorts. Journal of affective disorders.4022014;166:249-57.40349. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace404element research. 2012;145(3):286-90.40550. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving406depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan407Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40651. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice405for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo-410controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived41353. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.412evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42256. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422 <td></td> <td></td>		
2014;166:249-57.40349. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace404element research. 2012;145(3):286-90.40550. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving406depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan407Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40651. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice405for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostfavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived41353. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.412evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42256. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4222008;1237:52-61.<		
49. Yary T, Aazami S. Dietary intake of zinc was inversely associated with depression. Biological trace404element research. 2012;145(3):286-90.40550. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving406depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan407Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40651. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice405for depression maagement in patients with multiple sclerosis: a randomized, double-blind, placebo-410controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived413encurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the420evidence, potential mechanisms and implications. Nutr		
element research. 2012;145(3):286-90.40550. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40651. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived aneurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research. 4224222008;1237:52-61.42557. Krystal JH, Sanacora G		
50. Nazarinasab M, Behrouzian F, Salmanpour R. Evaluating the effectiveness of zinc sulfate in improving depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40051. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41052. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived sinew M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study. European journal of clinical nutrition. 2010;64(3):331.41855. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42150. Coniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research. 2008;1237:52-61.42257. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry. 2002;7(S1):S71.42658. Paoletti P, Vergnano A, Barbour B,		
depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan407Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40851. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice409for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo-410controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived413neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the422evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42356. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal42477. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antid		405
Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.40851. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice409for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo-410controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived413neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the420evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal42277. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(51):S71.427		406
51. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice409for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo-410controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived413neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the422evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal42277. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. N	depression symptoms in patients treated with selective serotonin reuptake inhibitors in Golestan	407
for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo- controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41052. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived413neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the420evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4222008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamater	Hospital in Ahvaz, Iran. Minerva Psichiatrica. 2017;58(3):156-61.	408
controlled clinical trial. Pharmacological Reports. 2015;67(3):606-9.41152. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived413neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the422evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	51. Salari S, Khomand P, Arasteh M, Yousefzamani B, Hassanzadeh K. Zinc sulphate: a reasonable choice	409
52. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc412supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived413neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the422evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	for depression management in patients with multiple sclerosis: a randomized, double-blind, placebo-	410
supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived413neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the420evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428		411
neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.41453. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments415efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the420evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4242008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.426	52. Ranjbar E, Shams J, Sabetkasaei M, M-Shirazi M, Rashidkhani B, Mostafavi A et al. Effects of zinc	412
<ul> <li>53. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments</li> <li>efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal</li> <li>of affective disorders. 2009;118(1-3):187-95.</li> <li>54. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.</li> <li>European journal of clinical nutrition. 2010;64(3):331.</li> <li>55. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the</li> <li>evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.</li> <li>56. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal</li> <li>precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.</li> <li>2008;1237:52-61.</li> <li>57. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA</li> <li>systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.</li> <li>2002;7(S1):S71.</li> <li>58. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.</li> </ul>	supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived	413
efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal416of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the420evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	neurotrophic factor in patients with major depression. Nutritional neuroscience. 2014;17(2):65-71.	414
of affective disorders. 2009;118(1-3):187-95.41754. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the420evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	53. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P et al. Zinc supplementation augments	415
54. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.418European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the420evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. Journal	416
European journal of clinical nutrition. 2010;64(3):331.41955. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42056. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research. 2008;1237:52-61.42057. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry. 2002;7(S1):S71.42058. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	of affective disorders. 2009;118(1-3):187-95.	417
55. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42056. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4222008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	54. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study.	418
evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	European journal of clinical nutrition. 2010;64(3):331.	419
evidence, potential mechanisms and implications. Nutrients. 2018;10(5):584.42156. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428	55. Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the	420
56. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal422precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428		421
precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. Brain research.4232008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428		422
2008;1237:52-61.42457. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428		423
57. Krystal JH, Sanacora G, Blumberg H, Anand A, Charney D, Marek G et al. Glutamate and GABA425systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428		424
systems as targets for novel antidepressant and mood-stabilizing treatments. Molecular psychiatry.4262002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428		425
2002;7(S1):S71.42758. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience.428		426
58. Paoletti P, Vergnano A, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience. 428		427
		428
2003,130(1),120-30. 423	2009;158(1):126-36.	429

59. Pittenger C, Sanacora G, Krystal JH. The NMDA receptor as a therapeutic target in major depressive	430
disorder. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological	431
Disorders). 2007;6(2):101-15.	432
60. Rosa AO, Lin J, Calixto JB, Santos ARS, Rodrigues ALS. Involvement of NMDA receptors and L-	433
arginine-nitric oxide pathway in the antidepressant-like effects of zinc in mice. Behavioural brain	434
research. 2003;144(1-2):87-93.	435
61. Chasapis CT, Loutsidou AC, Spiliopoulou CA, Stefanidou ME. Zinc and human health: an update.	436
Archives of toxicology. 2012;86(4):521-34.	437
62. Olfson M, Marcus SC, Tedeschi M, Wan GJ. Continuity of antidepressant treatment for adults with	438
depression in the United States. American Journal of Psychiatry. 2006;163(1):101-8.	439
63. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions.	440
Patient preference and adherence. 2012;6:369.	441

Legend of Tables	443
Table 1- Characteristics of observational studies evaluating the zinc-depression association	444
	445
<b>Table 2-</b> Characteristics of randomized controlled trials evaluating the effect of zincsupplementation on depression status.	446 447
	448
<b>Table 3</b> - Meta-analysis showing the effect of zinc supplementation on depression score based on several subgroups; all analyses were conducted using the random-effects model	449 450
<b>Table 4-</b> Effect of zinc supplementation on weighted mean difference controlling for age,         baseline depression score, dose of zinc supplementation and the study duration (conducted for         the random-effects model	451 452 453
	454

Author (Year)	Study name (Location)	Study design (follow-up year)	Number of participants (Age)	Depressive patients (N)	Zinc measurement	Depression scale	RR (95 % CI)	Factors adjusted for in analyses (Multivariable)
Jacka	$GOS^1$	Cross-sectional	1023	60	Dietary zinc	SCID-I/NP <sup>2</sup>	0.24 (0.08, 0.76)	Age, socioeconomic factors, physical activity, alcohol
(2012) [42]	(Australia)		(49-60)		intake			consumption, smoking, energy intake, BMI and supplementation
Jung	BASE-II <sup>3</sup>	Cross-sectional	1514 (<18)	238	Plasma Zinc	$CES-D^4$	0.67 (0.46, 0.97)	Sex, age, and body mass index, hypothyroidism, serum vitamin
(2017) [43]	(Germany)							D3and vitamin B12, plasma CRP, cognitive impairment, poor
								sleep quality, Morbidity index.
Lehto	KIHDRIS <sup>5</sup>	Prospective	2317	60	Dietary zinc	HPL <sup>6</sup>	0.94 (0.52, 1.69)	Age, baseline depression severity, smoking,
(2013) [44]	(Finland)	cohort (20 years)	(54.3)		intake			alcohol use, physical exercise and the use of dietary supplements
Li (2018)	NHANES <sup>7</sup>	Cross-sectional	14834	1367	Dietary zinc	PHQ-9 <sup>8</sup>	0.70 (0.47, 1.04)	Age, gender, BMI, race, educational level, smoking status,
[45]	(USA)		(18<)		intake			family income, work activity, recreational activity, hypertension,
								diabetes, and total daily energy intake
Maserejian	BACH <sup>9</sup>	Cross-sectional	3708	753	Dietary zinc	CES-D	0.72 (0.52, 0.93)	Age, race/ethnicity, socioeconomic status, BMI, physical
(2012) [46]	(USA)		(50.5)		intake			activity, smoking status, total energy intake, any
								antidepressant/antipsychotic medication use, cardiac disease, and
								arthritis/rheumatism

Table 1- Characteristics of observational studies evaluating the zinc-depression association

Miki (2015) [47]	FNHS <sup>10</sup> (Japan)	Cross-sectional	2006 (41)	557	Dietary zinc intake	CES-D	0.63 (0.45, 0.87)	Age, sex, and site, marital status, job grade, shift work, physical activity, smoking, alcohol consumption, intake of folate and vitamin C and vitamin B6 and vitamin B12 and polyunsaturated fatty acids
Vashum (2014) [48]	HCS <sup>11</sup> (Australia)	Prospective cohort (5)	2092 (<18)	270	Dietary zinc intake	CES-D	0.73 (0.44, 1.19)	Education, household income, hypertension, BMI, and energy intake
	ALSWH <sup>12</sup> (Australia)	Prospective cohort (6)	9738 (<18)	1830			0.70 (0.55, 0.90)	
Yary (2012) [49]	No brand (Malayia)	Cross-sectional	402 (32.54)	122	Dietary zinc intake	CES-D	0.50 (0.30, 0.84)	Sex, age, BMI, monthly expenses, close friends, living on campus, smoking, physical inactivity, education, and marital status
Das (2020) [39] Anbari (2020) [38]	CHAMP (Australia) No brand (Iran)	Prospective cohort (3) Cross-sectional	1705 (≥70) 297 (64)	83 125	Dietary zinc intake Serum/dietary zinc	GDS GDS	0.41 (0.20, 0.85) 1.26 (0.62, 2.34)	Age, body mass index, marital status, living arrangement, income, meal service, smoking, alcohol intake, comorbidity and energy, antidepressant medication age, BMI, sex, CVD, marital status, smoking, status, education, rheumatoid arthritis, hypertension, diabetes, hyperlipidemia, digestive disease
Nakamura (2019) [40]	Eat-Well (Japan)	Cross-sectional	2089 (18- 79)	144	Dietary zinc intake	Kessler's six item psychological distress scale (K6)	0.6 (0.32, 1.12)	age and sex, smoking, alcohol drinking, body mass index, shift work, and intake of Vitamin C, B6, B12, folic acid, and PUFA; medications for hypertension, hyperlipidemia, and diabetes

Nguyen	Shika study Cross-sectional	1423 (≥65) 280	Dietary zinc	GDS	0.58 (0.38, 0.9)	age, BMI, living status, having a job status, married status, smoking status, alcohol consumption, total energy, hypertension, diabetes, hyperlipidemia
(2019) [41]	(Japan)		intake			
1.0	Carlong Ostaonorosis Study 2 Str	natural Clinical Interview	For DSM IV TD Do	coorch Vore	on Non nations adition 2	Parlin Aging Study II: 4 Contar for Enidemiological

1 Geelong Osteoporosis Study; 2 Structured Clinical Interview for DSM-IV-TR Research Version Non-patient edition; 3 Berlin Aging Study II; 4 Center for Epidemiological Studies Depression scale; 5 Kuopio Ischemic Heart Disease Risk Factor Study; 6 Human Population Laboratory Depression Scale; 7 National Health and Nutrition Examination Survey; 8 Patient Health Questionnaire; 9 Boston Area Community Health Survey; 10 Furukawa Nutrition and Health Study; 11 Hunter Community Study; 12 Australian Longitudinal Study on Women's Health

The first author	Country	No. of	Design	Depression	Study	Depression	Zinc type	Control group	Results
(year)		participants		status	duration	scale	(Dose mg/day)	status	
		(Gender)			(week)				
Nazarinasab	Iran	Int <sup>1</sup> : 29, Cont <sup>2</sup> :	Parallel	Depressed	8	BDI II <sup>3</sup>	Zinc sulfate	Anti-depressant	Significant effect on Beck score in in combination
(2017) [50]		29		patients			(25)	drug	with selective serotonin inhibitors reduces depression
		(Both)							
Nowak	Poland	Int:6, Cont:8	Parallel	Depressed	12	HDRS <sup>4</sup> and	Zinc (25)	Anti-depressant	Significant effect on Beck and HDS score in patients
(2003) [19]		(Both)		patients		BDI II		drug	with major depression
-	-		~						
Ranjbar, (2013)	Iran	Int:21, Cont:17	Parallel	Depressed	12	BDI II	Zinc sulfate	Anti-depressant	Significant effect on Beck score together with the
[20]		(Both)		patients			(25)	drug	antidepressant drug in patients with major depression
Ranjbar, (2014 )	Iran	Int:21, Cont:17	Parallel	Depressed	12	HDRS	Zinc sulfate	Anti-depressant	Significant effect on HDRS score together with
[52]		(Both)		patients			(25)	drug	antidepressant drug in patients with major depression
				•				-	
Salari, (2015)	Iran	Int:21, Cont:22	Parallel	Depressed	12	BDI II	Zinc sulfate	Placebo	Significant effect on Beck score in MS patients with
[51]		(Both)		patients			(220)		major depression
Siwek (2009)	Poland	Int:30, Cont:30	Parallel	Danragad	12	HDRS, BDI	zina hudro	Anti donraccont	No significant effect in antidepressant treatment
. ,	Folaliu	,	Falallel	Depressed	12	II, $CGI^5$ and	zinc hydro	Anti-depressant	
[53]		(Both)		patients		MADRS <sup>6</sup>	aspartate (25)	drug	nonresistant patients, significant effect in
						MADKS			antidepressant treatment resistant patients
Solati, (2015)	Iran	Int:22, Cont:24	Parallel	Both	12	BDI II	Zinc gluconate	Placebo	Zinc monotherapy improves mood in overweight or
[30]		(Both)					(30)		obese subjects
Yosaee (2018)	Iran	Int:30, Cont:30	Parallel	Depressed	12	BDI II	Zinc gluconate	Placebo	Significant effect on Beck score in depressed patients
[31]		(Both)		patients			(30)		

 Table 2- Characteristics of randomized controlled trials evaluating the effect of zinc supplementation on depression status.

1. intervention, 2. control, 3. Beck Depression Inventory, 4. Hamilton Depreaaion Rating Scale, 5. Clinical Global Impression, 6. Montgomery-Asberg Depression Rating Scale

	Number	Meta-analys	sis		Hetero	geneity	
Study group	Number – of studies	(95% CI)	<i>P</i> value	Q statistic	P within group	I <sup>2</sup> (%)	P between group
Overall	7	-4.15 (-6.56, -1.75)	< 0.001	30.11	<0.001	80.1	
Depression status							
Depressed patients	6	-4.58 (-7.55, -1.60)	0.003	30.06	< 0.001	83.4	0.816
Mixed population	1	-2.92 (-5.39, -0.44)	0.021	0.00			
Depression scale							
Beck	7	-4.16 (-6.56, -1.75)	< 0.001	30.11	< 0.001	80.1	0.949
Hamilton	3	-8.04 (-15.00, -1.07)	0.024	20.99	< 0.001	90.5	
Duration							
Shorter period ( $\leq 12$ weeks)	6	-4.73 (-8.25, -1.19)	0.009	29.99	< 0.001	83.3	0.728
Longer period (> 12 weeks)	1	-3.32 (-4.40, -2.24)	< 0.001	0.00			
zinc prescription							
Monotherapy	3	-5.05 (-7.55, -2.54)	< 0.001	4.35	0.114	54	0.024
Adjunctive therapy	4	-3.70 (-7.80, 0.39)	0.076	20.66	< 0.001	85.5	
Control group status							
Without antidepressant	3	-5.05 (-7.55, -2.54)	< 0.001	4.35	0.114	54	0.024
With antidepressants	4	-3.70 (-7.80, 0.39)	0.076	20.66	< 0.001	85.5	

**Table 3-** Meta-analysis showing the effect of zinc supplementation on depression score based on several subgroups; all analyses were conducted using the random-effects model

Variable	Estimated coefficient	Standard error	I-squared residual	P- Value
Age	-0.134	0.037	83.50	0.005
Zinc supplementation dose (mg/d)	-0.178	0.049	80.95	0.006
Duration (weeks)	-0.321	0.116	8528	0.015
Baseline depression score	-0.195	0.054	85.76	0.006

**Table 4-** Effect of zinc supplementation on weighted mean difference controlling for age, baseline depression score, dose of zinc supplementation and the study duration (conducted for the random-effects model)

Legend of Figures	1
Figure 1- Effect of zinc supplementation on depression status in randomized controlled trials	2
Figure 2- Relative risk (RR) of depression status for the highest versus lowest category of zinc	3
intake among prospective cohort studies.	4
Figure 3- Relative risk (RR) of depression status for the highest versus lowest category of zinc	5
status among cross-sectional studies.	6
	7

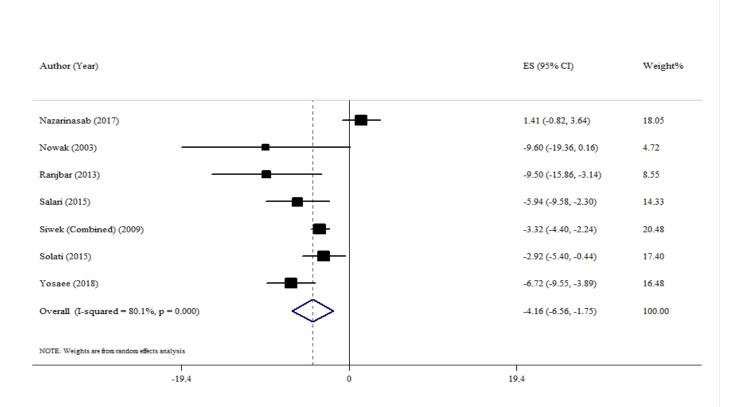
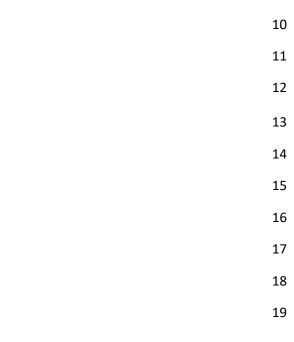
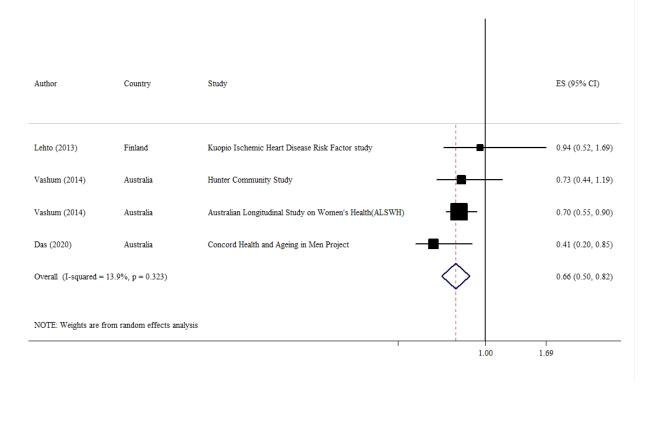


Figure 1- Effect of zinc supplementation on depression status in randomized controlled trials







**Figure 2-** Relative risk (RR) of depression status for the highest versus lowest category of zinc intake among prospective cohort studies.

Author	Country	Study	ES (95% CI)
Dietary intake			
Jacka (2012)	Australia	Geelong Osteoporosis Study	0.24 (0.08, 0.76
Li (2017)	USA	National Health and Nutrition Examination Survey	0.70 (0.47, 1.04
Maserejian (2012)	USA	Boston AreaCommunity Health (BACH)	0.72 (0.52, 0.93)
Miki (2015)	Japan	Furukawa Nutrition and Health Study	0.63 (0.45, 0.87)
Yary (2012)	Iran	Iranian postgraduate students in Malaysia	0.50 (0.30, 0.84)
Anbari-Nogyni (2020)	Iran	Old Population	1.26 (0.62, 2.34)
Nakamura (2019)	Japan	Eating Habit and Well-Being Study	0.60 (0.32, 1.12)
Nguyen (2019)	Japan	Shika Study	0.58 (0.38, 0.90)
Subtotal (I-squared = 21.9%, p = 0.256)			0.60 (0.49, 0.72)
Serum			
Jung (2017)	Germany	Berlin Aging Study II	0.67 (0.46, 0.97)
Anbari-Nogyni (2020)	Iran	Old Population	0.49 (0.25, 0.96)
Subtotal (I-squared = 0.0%	0.61 (0.40, 0.82)		
Overall (I-squared = 6.3%, p = 0.383)			0.61 (0.51, 0.70)
NOTE: Weights are from ra	andom effects analys	is	

**Figure 3-** Relative risk (RR) of depression status for the highest versus lowest category of zinc status among cross-sectional studies.