Is there an Association between Blood Nutrient Levels and Depression? A Systematic Review

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Abstract: This review presents a summary of the available evidence on the relationship between blood nutrient levels and depression. Sixty relevant articles were identified from database searches of studies published from 1994 to 2013. Studies reviewed demonstrated fair support for an association between blood levels of vitamin D and iron with depression, and limited support for an association between blood levels of omega-3 polyunsaturated fatty acids and zinc with depression. Conflicting results were found for other nutrients of interest such as folate, vitamin B12, magnesium and antioxidants. Five prospective cohort studies reviewed here have demonstrated that for some nutrients (vitamin D, iron, folate, omega-3 fatty acids) low blood nutrient levels precede the development of depression. There is insufficient evidence to establish a causal relationship, and it appears likely that that the relationship between blood nutrient levels and depression is bi-directional. There is also limited evidence to demonstrate that low blood nutrient levels are related to dietary intake. Further research is needed to elucidate whether the associations between blood nutrient levels and depression are related to dietary intake. Randomised controlled trials investigating both nutrient supplementation and specific dietary patterns are needed to provide evidence to support dietary recommendations for the prevention and management of depressive disorders.

Keywords: Nutrients, nutrition, depression, systematic review.

INTRODUCTION

Depression is the leading cause of disability worldwide, with over 350 million people affected by depression globally [1]. Depression commonly co-occurs with a number of other conditions including other mental disorders, chronic physical conditions, and communicable diseases [2]. Usual treatment for depression includes medication and psychological intervention [3]. There is increasing scope for the use of lifestyle interventions including physical activity and nutrition in the management of depression [4, 5].

The mechanism underlying the relationship between nutrients and depression is complicated and still largely unknown. Many nutrients have known roles in brain function which may be related to depression. Antioxidants protect against oxidative damage to cell membranes and may also prevent depression by improving serotonin levels [6]. Omega-3 polyunsaturated fatty acids are involved in neurological development, are structural components of brain cells and facilitate effective neurotransmission [6]. They contribute to the anti-inflammatory response and minimise oxidative damage which may play a role in the prevention of depression [6]. The B vitamins are involved in neurotransmitter synthesis and play a role in the methylation cycle and one-carbon metabolism [6]. They may prevent depression by limiting homocysteine-induced oxidative stress [6]. Vitamin D is involved in the modulation of neurotransmitters and regulation of calcium concentration to avoid toxicity [7-10]. Iron is involved in neurotransmitter synthesis, axon myelination and oxygen transport, and appropriate iron levels can prevent lethargy, apathy and difficulty concentrating [11-13]. For a detailed review of the role of nutrients in brain function and mental health, refer to Parletta *et al*. [6].

The relationship between nutrition and depression is being studied with increasing interest, but there are still a limited number of studies that have investigated the relationship between blood nutrient levels with depression. Early studies that were published often had small numbers of participants or were limited to specific groups, and it was previously suggested that there were too few controlled trials on this topic to warrant a meta-analysis [14]. The aim of this systematic review is to identify and describe the results of studies published in the past 20 years evaluating an association between blood nutrient levels and depression.

METHODS

A preliminary search was conducted by the authors using Scopus, PubMed, and Web of Science for articles with keywords “depression” or “depressive symptoms” in conjunction with “nutritional deficiencies” “serum nutrient concentrations” and “blood nutrient levels”. This initial search retrieved 333 studies after limiting the search terms to English language articles published between January 1994 and October 2013.

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After removing duplicates and screening articles for relevance and eligibility criteria, 20 studies were included (Figure **1**).

The initial search strategy identified several nutrients of interest (as listed in Table **1** summary). A subsequent search was conducted to identify additional articles that address the association between depression and each of the identified nutrients. The search terms in this case were "depression" or "depressive symptoms" and the nutrient of interest. This search strategy generated an additional 1377 English language studies published between January 1994 and October 2013. After removing duplicates and screening articles, an additional 16 articles were identified for inclusion (Figure **1**). Cross-checking of references cited in these articles resulted in an additional 24 studies included.

Review and selection of articles was performed independently by each of the authors. Selection of articles was restricted to those in which the study subjects were human and nutrient levels measured in the blood or other tissues were assessed and compared to the prevalence of depressive disorders or depressive symptoms. There was no restriction placed on age of study subjects as depression can affect people of all ages. Studies published in the twenty years from January 1994 to October 2013 were included in this review. While many earlier studies are available, especially regarding folate and depression, these studies were often scoping in nature, did not use appropriate control comparisons and lacked methodological detail to determine the overall quality of the study. Studies focusing on groups with specific physical or mental illness other than depression were not included in this review. Published reviews were not

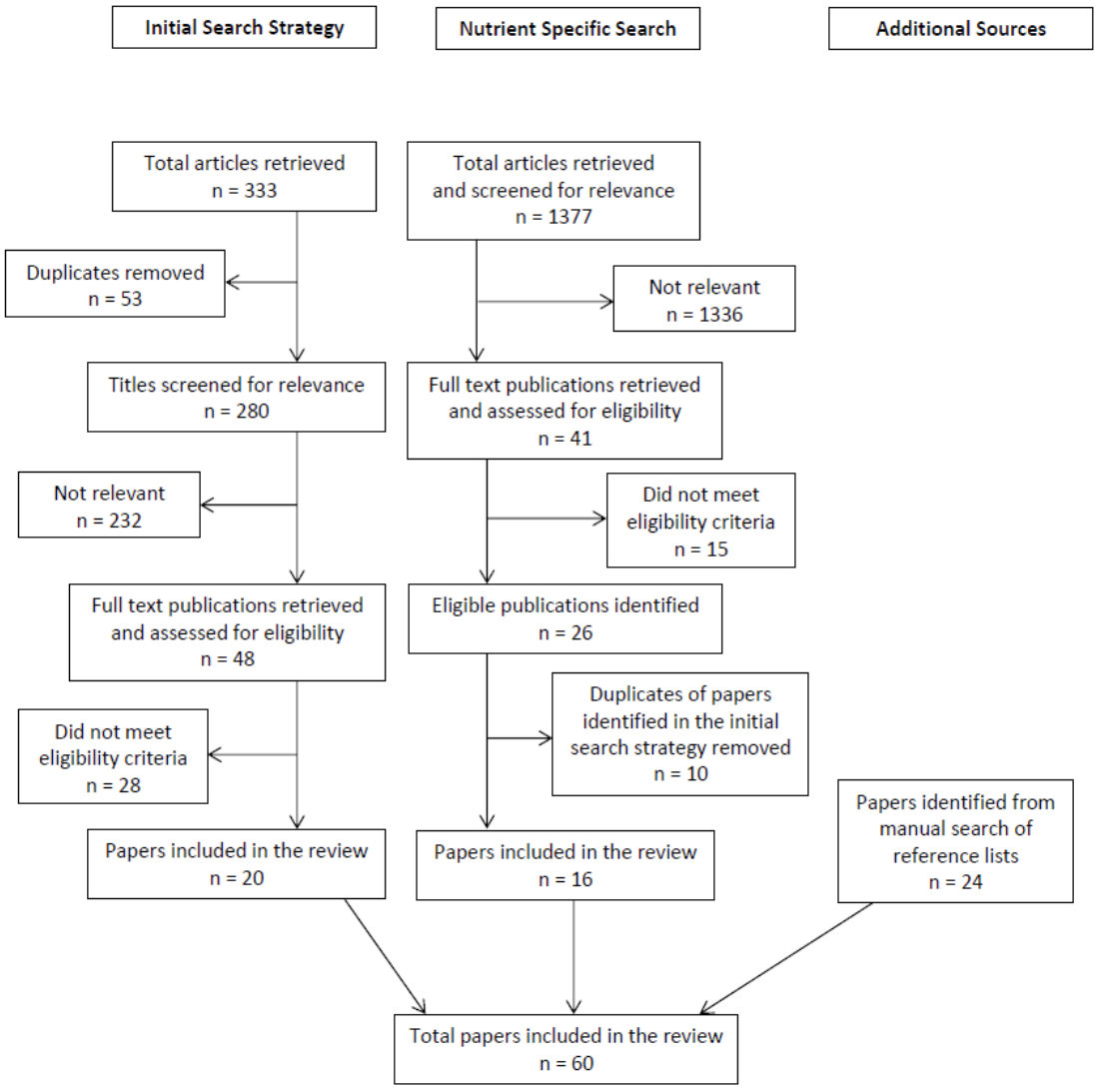

Figure 1: Literature search process.

synthesised with the other papers described here, but were screened for additional relevant studies. A total of 60 studies were used to assess the body of evidence surrounding the association between nutrient levels and depression (Figure **1**).

A qualitative assessment of data is presented as the degree of variability across the eligible studies prohibited a quantitative meta-analysis of the research. All studies identified have been summarised in Table **1**. Studies were rated for quality using the Academy of Nutrition and Dietetics quality criteria checklist [15]. This scale is used to rate the methodological quality of published work as 'positive', 'neutral' or 'negative'. The strength of the evidence was graded and reported based on the Academy of Nutrition and Dietetics grade definitions [15]. These definitions rate the strength of the evidence as 'good' for studies of strong design, 'fair' for studies of strong design with some inconsistency in results or minor design flaws, and 'limited' for results from a small number of studies with weak design.

RESULTS

Of 60 papers summarised here, 42 were assigned a quality rating of neutral. In the majority of cases, the assignment of a neutral rather than positive quality rating was related to the sample where study populations may have been biased, selected for convenience, and not a representative sample of the relevant population. In some cases, insufficient detail was provided to determine whether study groups were comparable. Some papers did not sufficiently address potential confounding variables.

The studies identified for inclusion in this review include 32 cross-sectional studies, eight prospective cohort studies, 17 case-control studies, two randomised controlled trials and three case series. Some studies employed more than one experimental design. The sample populations varied greatly with research conducted across North America, Europe, Asia, Africa and Australia, including both men and women from 15 to 95 years of age. Studies used several different measures of depression. Several case-control studies considered clinical diagnosis of depression only and did not apply a tool to measure the severity of depressive symptoms. Nutrient levels were sampled from a number of tissues including plasma, serum, erythrocytes and erythrocyte membranes. A number of different biomarkers were used; for example iron status was measured using haemoglobin levels, transferrin saturation and ferritin, with different biomarkers being used in different studies. A summary of study characteristics and findings is presented in Table **1**. The summary following Table **1** presents the number of studies that demonstrate a positive, inverse, or lack of association between nutrient level and depression. Studies with variable evidence (for example, an association in either males or females only, or an association with at least one but not all biomarkers of a particular nutrient) have been placed within the most relevant category based on the overall evidence presented.

Fatty Acids

Serum or red blood cell concentrations of omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been repeatedly demonstrated to be lower in individuals with depression and a strong correlation has been found between n-3 PUFA levels and severity of depression. In this review, total n-3 PUFA levels were inversely associated with depressive symtpoms in seven of 12 studies. Specific n-3 PUFAs identified to be inversely associated with depressive symtpoms include ALA [19], EPA [17, 19, 22], DHA [17-21, 24], and DPA [17, 19]. The ratio of n-3:n-6 PUFAs may also play a role, with an inverse association with depressive symptoms found in six of nine studies. A 2010 meta-analysis of studies investigating the association between fatty acid levels and depression found that levels of EPA, DHA and total n-3 PUFAs were significantly lower in patients with depression when compared to controls (effect size (ES)= -.18, $p = .004$; ES = -.35, $p = .0002$; ES = -.51, $p = .0001$) [76].

Vitamins

There have been few recent studies investigating the relationship between thiamine (vitamin B1) and riboflavin (vitamin B2) with depression. This review identified only one study that looked at this relationship [38]. Neither of these nutrients were found to have a significant inverse association between plasma nutrient levels and depressive symptoms.

The first studies demonstrating an association between folate levels and depression were published in the 1960s [76]. The early studies were conducted primarily with hospital inpatients. Since then, the relationship has been studied in a variety of population groups. Studies within the past twenty years continue to support the inverse association between folate levels and depression, although no significant relationship

Table 1: Studies Investigating the Association between Blood Nutrient Levels and Depression

Publication	Country	Study type	Quality rating	Study population	Measure of depression	Sampling tissue	Nutrient	Finding
Maes 1996 [16]	Belgium	Case-control	Neutral	24 healthy volunteers and 50 depressed patients	Hamilton Depression Rating Scale	Serum	Phospholipids:	
							Total n-3	0
							Total n-6	0
							n-3:n-6	0
							Cholesterol esters:	
							Total n-3	-
							n-3:n-6	-
Edwards 1998 [17]	UK	Case-control	Neutral	10 patients with depression and 14 healthy matched controls	Beck Depression Inventory	Erythrocyte membranes	Total n-3 PUFA	-
							Total n-6 PUFA	0
							ALA	0
							EPA	-
							DPA	-
							DHA	-
Peet 1998 [18]	UK	Case-control	Neutral	15 patients with depression and 15 healthy controls aged 18–65 years	Montgomery Asberg Depression Rating Scale	Erythrocyte membranes	Total n-3 PUFA	-
							DHA	-
							EPA	0
							Total n-6 PUFA	0
							n-3:n-6 ratio	0
Maes 1999 [19]	Belgium	Case-control	Neutral	34 in patients with major depression and 14 healthy volunteers	Hamilton Depression Rating Scale	Serum	Cholesterol esters:	
							Total n-6 PUFA	-
							Total n-3 PUFA	-
							ALA	-
							EPA	-
							n-3:n-6 ratio	-
							Phospholipids:	
							Total n-6 PUFA	0
							Total n-3 PUFA	-
							EPA	-
							DPA	-
							DHA	-
							n-3:n-6 ratio	0
							Zinc	-
De Vriese 2003 [20]	Belgium	Prospective cohort	Neutral	48 pregnant women (measures taken after delivery); 10/48 developed post-partum depression	Diagnostic telephone interview (6-10 months post-partum)	Serum	DHA	-
							Total n-3	-
							n-3:n-6 ratio	-
Tiemeier 2003 [21]	Netherlands	Case-control	Positive	264 subjects with depressive disorders and 461 reference subjects older than 60 years of age	Center for Epidemiological Studies Depression Scale	Plasma	Total n-6 PUFA	0
							Total n-3 PUFA	0
							DHA	-
							n-3:n-6 ratio	-
Feart 2008 [22]	France	Cross-sectional	Positive	1390 adults over 65 years of age participating in the Three-City Study	Center for Epidemiologic Depression Scale	Plasma	EPA	-
							All other individual fatty acids	0
Dinan 2009 [23]	Ireland	Case-control	Neutral	58 subjects aged 28-57 years; 20 with major depression who did not respond to an SSRI, 14 who had responded to an SSRI, and 24 healthy controls	Hamilton Depression Rating Scale	Plasma	AA	+

(Table 1). Continued.

Publication	Country	Study type	Quality rating	Study population	Measure of depression	Sampling tissue	Nutrient	Finding
Rees 2009 [24]	Australia	Case-control	Positive	16 depressed and 22 non-depressed women over age 21 years in the third trimester of pregnancy	Edinburgh Depression Scale, 17-item Hamilton Depression Rating Scale and Montgomery–Asberg Depression Rating Scale	Plasma	DHA Total n-3 n-3:n-6 ratio	- - -
Riemer 2010 [25]	Germany	Case-control	Neutral	36 inpatients with major depression, 37 inpatients with somatization syndrome, 40 patients with somatization syndrome and major depression, 37 healthy volunteers	Beck Depression Inventory	Serum	n-3 PUFAs n-3:n-6	- -
Fava 1997 [26]	USA	Case series (based on baseline results of a prospective cohort study)	Neutral	213 outpatients aged 18–65 years with major depressive disorder	Hamilton Depression Rating Scale	Serum	Folate Vitamin B12 Homocysteine	- 0 0
Bottiglieri 2000 [27]	UK	Case-control	Neutral	46 inpatients with severe depression, 18 healthy volunteers and 20 patients with neurological disorders	Clinical diagnosis	Serum, erythrocyte and CSF serum	Folate Vitamin B12 Homocysteine	- 0 +
Lindeman 2000 [28]	USA	Cross-sectional	Neutral	883 men and women aged over 65 years participating in the New Mexico Elder Health Survey	Geriatric Depression Scale	Serum	Folate Vitamin B12 Vitamin C	0 0 0
Tiemeier 2002 [29]	Netherlands	Cross-sectional	Positive	278 community dwelling adults with depression aged over 55 years and 416 reference subjects participating in the Rotterdam Study	Center for Epidemiological Studies Depression Scale	Serum	Folate Homocysteine Vitamin B12	0 0 -
Bjelland 2003 [30]	Norway	Cross-sectional	Neutral	2291 men and 2558 women aged 46 to 49 years, and 1868 men and 2470 women aged 70-74 years	Hospital Anxiety and Depression Scale	Plasma	Vitamin B12 Homocysteine Folate	0 + -(middle aged women only) 0 (all other groups)
Morris 2003 [31]	USA	Cross-sectional	Positive	2948 men and women aged 15-39 years participating in the National Health and Nutrition Examination Studies	Diagnostic Interview Schedule	Serum & Erythrocytes	Folate Homocysteine	- 0
Hvas 2004 [32]	Denmark	Cross-sectional	Neutral	140 participants from an earlier study aged 19-92 years (mean age 72 years)	Major Depression Inventory	Plasma Plasma Erythrocyte	Vitamin B6 Vitamin B12 Folate Homocysteine	- 0 0 0

(Table 1). Continued.

Publication	Country	Study type	Quality rating	Study population	Measure of depression	Sampling tissue	Nutrient	Finding
Beydoun 2010 [33]	USA	Cross-sectional	Positive	2524 participants in the National Health and Nutrition Examination Survey aged 20–85 years	Patient Health Questionnaire	Serum	Folate Vitamin B12 Homocysteine	- 0 0
Forti 2010 [34]	Italy	Cross-sectional	Neutral	584 participants over age 65 years from the Conselice Study of Brain Aging	Geriatric Depression Scale	Serum	Vitamin B12 Folate Homocysteine	0 0 + (women) 0 (men)
Watanabe 2010 [35]	Japan	Cross-sectional	Neutral	86 pregnant women in the first trimester who presented to an antenatal clinic	Center for Epidemiologic Studies Depression Scale	Serum	Folate Homocysteine	0 0
Moorthy 2012 [36]	USA	Cross-Sectional	Positive	Community-dwelling adults participating in the Boston Puerto Rican Health Study aged 45–75 years (n = 939) and the Nutrition, Aging, and Memory in Elders study aged over 60 years (n = 1017)	Center for Epidemiological Studies Depression Scale	Plasma	Folate Vitamin B6 Vitamin B12 Homocysteine	0 0 - 0
Nanri 2012 [37]	Japan	Cross-sectional and prospective cohort	Neutral	545 full time municipal employees participating in a health survey (272 with data from previous survey for prospective cohort)	Center for Epidemiologic Studies Depression Scale	Serum	Folate	-
Pan 2012 [38]	Taiwan	Cross-sectional	Neutral	1371 community-dwelling residents aged over 65 years	Five items from the Medical Outcomes Study 36-Item Short-Form Health Survey	Plasma	Iron (haemoglobin) Vitamin B1 Vitamin B2 Vitamin B6 Vitamin B12 Folate	- 0 0 - 0 0
Robinson 2012 [39]	Ireland	Cross-sectional	Neutral	466 community dwelling elderly participating in the Dublin Healthy Ageing Study	Center for Epidemiologic Studies Depression Scale	Serum	Vitamin B12 Folate Homocysteine	- 0 0
Jorde 2006 [7]	Norway	Cross-sectional	Neutral	21 subjects with secondary hyper-parathyroidism (not due to renal failure) and 63 healthy controls	Beck Depression Inventory	Serum	Vitamin D	-
Hoogendijk2008 [40]	Netherlands	Prospective cohort	Positive	1282 community residents aged 65-95 years participating in the Longitudinal Aging Study Amsterdam	Center for Epidemiologic Studies Depression scale	Serum	Vitamin D	-
Pan2009 [41]	China	Cross-sectional	Positive	3262 community residence aged 50-70 years	Center for Epidemiological Studies of Depression Scale	Plasma	Vitamin D	0

(Table 1). Continued.

Publication	Country	Study type	Quality rating	Study population	Measure of depression	Sampling tissue	Nutrient	Finding
Ganji 2010 [42]	USA	Cross-sectional	Positive	7970 men and women aged 15-39 years	Diagnostic Interview Schedule	Serum	Vitamin D	-
Milaneschi 2010 [43]	Italy	Prospective cohort	Positive	531 women and 423 men aged 65 years and older participating in the InCHIANTI (Invecchiare in Chianti, aging in the Chianti area) Study	Center for Epidemiological Studies Depression Scale	Serum	Vitamin D	-(females) 0 (males)
Murphy 2010 [44]	USA	Cross-sectional	Neutral	97 postpartum women attending seven monthly postnatal visits	Edinburgh Postpartum Depression Scale	Serum	Vitamin D	-
Stewart 2010 [45]	UK	Cross-sectional	Positive	2070 participants aged over 65 years who had participated in the 2005 Health Survey for England	Geriatric Depression Scale	Serum	Vitamin D	-
Zhao 2010 [46]	USA	Cross-sectional	Neutral	3916 adults aged 20 years or older participating in the 2005–6 National Health and Nutrition Examination Survey	Patient Health Questionnaire	Serum	Vitamin D	0
Kjaergaard 2011 [47]	Norway	Cross-sectional	Positive	1966 smokers and 8120 non-smokers ranging in age from 30-85 years participating in The Tromsø Study	Hopkins Symptoms Check List 10	Serum	Vitamin D	-
Lasaite 2011 [48]	Lithuania	Cross-sectional	Neutral	130 healthy male military conscripts and medical students aged 18-26 years	Profile of Mood States (POMS) questionnaire and Hospital Anxiety and Depression Scale	Serum	Vitamin D	- (one POMS subscale only) 0 (all other subscales)
Hogberg 2012 [49]	Sweden	Case series	Neutral	54 depressed adolescents aged 10-19 years	Mood and Feelings Questionnaire	Serum	Vitamin D	-
Kjaergaard2012 [50]	Norway	Nested case-control and randomised controlled trial	Positive	230 subjects with low 25(OH)D levels and 114 controls with adequate 25(OH)D levels, aged between 30-75 years participating in the Tromsø study	Beck Depression Inventory, Hospital Anxiety and Depression Scale, Seasonal Pattern Assessment Scale and Montgomery–Asberg Depression Rating Scale	Serum	Vitamin D	-

(Table 1). Continued.

Publication	Country	Study type	Quality rating	Study population	Measure of depression	Sampling tissue	Nutrient	Finding
Lapid 2013 [51]	USA	Cross-sectional	Neutral	1618 primary care patients aged over 60 years	Clinical diagnosis of depression	serum 25(OH)D	Vitamin D	-
Shibata 1999 [52]	Japan	Cross-sectional	Neutral	504 community dwelling adults aged over 65 years participating in the Tokyo Metropolitan Institute of Gerontology Longitudinal Interdisciplinary Study on Aging	Geriatric Depression Scale	Serum	Vitamin E	0
Maes 2000 [53]	Belgium	Case-control	Neutral	42 patients with major depression and 26 healthy volunteers	Hamilton Depression Rating Scale	Serum	Vitamin E	-
Tiemeier 2002 [54]	Netherlands	Cross-sectional	Positive	262 community dwelling adults with depression aged over 55 years and 459 reference subjects participating in the Rotterdam Study	Center for Epidemiological Studies Depression Scale	Plasma	Vitamin E	0
Owen 2005 [55]	Australia	Cross-sectional	Neutral	29 female and 20 male outpatients with depression aged 19-70 years	Beck Depression Inventory	Plasma	Vitamin E	-
Beydoun 2013 [56]	USA	Cross-sectional	Positive	1798 adults aged 20-85 years participating in the National Health and Nutritional Examination Surveys	Patient Health Questionnaire	Serum	Carotenoids Retinol Vitamin C Vitamin E	- 0 0 0
Maes 1996 [57]	Belgium	Case-control	Neutral	38 patients with major depression and 15 healthy volunteers	Hamilton Depression Rating Scale	Serum	Iron Transferrin Erythrocyte count Haematocrit Haemoglobin	- - - - -
Rangan 1998 [58]	Australia	Cross-sectional	Neutral	255 females students aged 15-30 years	General Health Questionnaire	Serum	Iron Haemoglobin Ferritin Transferrin receptor Transferrin saturation	0 - 0 0 0
Hunt 1999 [59]	USA	Cross-sectional	Neutral	365 non-pregnant premenopausal women aged 20 to 45 years	Minnesota Multiphasic Personality Inventory	Serum	Iron (transferrin saturation) (haemoglobin) (ferritin)	- 0 0
Corwin 2003 [60]	USA	Prospective cohort	Neutral	37 females who had given birth with no complication	Center for Epidemiological Studies Depression Scale	Erythrocytes	Iron (haemoglobin)	-
Beard 2005 [61]	South Africa	Case-control (based on baseline results of a prospective randomized controlled trial)	Neutral	81 post-partum women aged 18-30 years	Edinburgh Postnatal Depression Scale	Erythrocytes	Iron (based on haemoglobin levels)	0
Shariatpanaahi2007 [62]	Iran	Cross-sectional	Neutral	192 female medical students	Beck Depression Inventory	Serum	Iron (ferritin)	-

(Table 1). Continued.

Publication	Country	Study type	Quality rating	Study population	Measure of depression	Sampling tissue	Nutrient	Finding
Alves de Rezende 2009 [63]	Brazil	Cross-sectional	Neutral	100 nursing home residents aged over 60 years	Short version of the Geriatric Depression Scale	Erythrocytes	Iron (haemoglobin & haematocrit)	- (males) 0 (females)
Albacar 2011 [64]	Spain	Prospective cohort	Positive	729 postpartum women participating in a large multicentre prospective study (measures taken 48 hours after delivery); 65/729 developed post-partum depression	Edinburgh Postnatal Depression Scale	Serum Serum Plasma Serum	Transferrin Ferritin Free iron Transferrin saturation	- 0 0 0
Yi 2011 [65]	Japan	Prospective cohort	Neutral	312 men and 216 women	Center for Epidemiological Studies Depression Scale	Serum	Iron (ferritin)	0 (women) -(men)
Stewart 2012 [66]	UK	Cross-sectional	Positive	1875 participants aged 65 years and older who had participated in the 2005 Health Survey for England	Geriatric Depression Scale	Serum	Iron (haemoglobin, ferritin, and transferrin receptor levels)	-
Maes 1994 [67]	Belgium	Case-control	Neutral	48 patients with depression and 32 healthy volunteers	Beck Depression Score and Zung Depression Score	Serum	Zinc	-
Maes 1997 [68]	Belgium	Case-control	Neutral	31 patients with major depression and 15 healthy volunteers	Hamilton Depression Rating Scale	Serum	Zinc Copper	- 0
Maes1999 [69]	Belgium	Case-control	Neutral	48 patients with major depression and 15 healthy age and sex matched controls	Clinical diagnosis	Serum	Zinc	-
Siwek 2010 [70]	Poland	Case-control	Neutral	66 outpatients aged 18-55 years with major depression and 25 healthy controls	Montgomery–Asberg Depression Rating Scale	Serum	Zinc	-
Kamei 1998 [71]	Japan	Case-control	Neutral	12 patients with major depression, 19 patients in remission from major depression, and 20 healthy controls	Hamilton Depression Rating Scale	Erythrocytes	Calcium Magnesium Sodium Potassium	- 0 0 0
Singh 2011 [72]	India	Case-control	Neutral	100 patients with depression aged 35-45 years and 40 age matched healthy volunteer controls	Diagnostic interview and Hamilton Depression Rating Scale	Serum	Sodium Potassium Magnesium Calcium	0 0 - -
Camardese 2012 [73]	Italy	Case series	Neutral	123 outpatients during a major depressive episode	Hamilton Depression Rating Scale	Plasma	Magnesium	0
Bodnar 2012 [74]	USA	Cross-sectional	Neutral	135 women who enrolled in the Antidepressant Use During Pregnancy (ADUP) Study at <20 weeks' gestation and had a diagnosis of MDD	Hamilton Rating Scale for Depression	Erythrocyte Plasma Serum	n-3 PUFA Folate Vitamin C Vitamin D Retinol Vitamin E Carotenoids Iron (ferritin and soluble transferrin receptors)	0 0 0 0 0 0 0 0

AA = Arachidonic acid (n-6); ALA = α-Linolenic acid (n-3); EPA = Eicosapentaenoic acid (n-3); DPA = Docosapentaenoic acid (n-3); DHA = Docosahexaenoic acid (n-3); n-3 PUFA = omega-3 polyunsaturated fatty acids; n-6 PUFA = omega-6 polyunsaturated fatty acids.

(Table 1). Continued.

Summary

Nutrient	-	0	+
n-3 PUFA	7	5	0
n-6 PUFA	1	4	1
n-3:n-6	6	3	0
Vitamin A	1	1	0
Vitamin C	0	3	0
Vitamin E	2	4	0
Vitamin B1	0	1	0
Vitamin B2	0	1	0
Folate	5	10	0
Vitamin B6	2	1	0
Vitamin B12	3	8	0
Homocysteine	0	8	3
Vitamin D	10	4	0
Iron	10	2	0
Zinc	5	0	0
Copper	0	1	0
Magnesium	1	2	0
Calcium	2	0	0
Sodium	0	2	0
Potassium	0	2	0

+ = nutrientlevels associated with symptoms of depression.
0 = no significant association.
- = nutrientlevels inversely associated with symptoms of depression.

was found in ten out of the fifteen studies presented in this review. The studies with the largest (n > 2000) and most generalisable sample populations were amongst those that found an inverse relationship between folate levels and depressive symptoms [30, 31, 33]. Folate and vitamin B12 share a functional role in the brain as both are involved in the production of monoamine neurotransmitters. Fewer studies have investigated the association between vitamin B12 levels and depression, with only three of 11 studies presented in this review demonstrating a significant inverse relationship between vitamin B12 levels and depressive symptoms. Tiemeier *et al*. [29] found that the severity of depression was related to serum vitamin B12 levels, with depressive disorders nearly 70% more likely among participants with vitamin B12 deficiency (OR = 1.69, 95% CI: 1.10-2.56, p = 0.02). Homocysteine, a biomarker of B vitamin status that is elevated when folate, vitamin B12 and vitamin B6 are reduced, was also found to be associated with depression in only three of 11 studies; homocysteine levels were positively associated with depressive symptoms in two studies [30, 34], and with diagnosis of depression in another [27]. Low levels of vitamin B6 were associated with depressive symptoms in two of three studies included in this review.

Recently, the greatest increase in research in this area has been surrounding the relationship between vitamin D and depression. Fourteen studies are presented in this review, and ten of these have been published in the past three years. Ten of fourteen studies have demonstrated an inverse association between vitamin D levels and depression; two studies found an association between low vitamin D levels and diagnosis of depression, and eight found an inverse association between vitamin D levels and depressive symptoms. In an American national survey, young adults aged 15-39 years with vitamin D deficiency were found to have a higher likelihood of having a current depressive episode than those with vitamin D sufficiency (OR = 2.01, 95% CI: 1.25-3.24, p < 0.001) [42]. The evidence surrounding vitamin D and depression is quite compelling given that the evidence is based on large sample sizes (seven studies with n > 1000), a variety of age groups including adolescents and older adults, and in studies conducted across three continents in the northern hemisphere. These results

are likely to have clinical relevance for the prevention and treatment of seasonal onset of depressive symptoms [77].

A small number of studies have also investigated antioxidant vitamins A, C and E. Only two studies identified in this review investigated the relationship between vitamin A levels and depression [56, 74]. Retinol was not associated with depression in either study, but serum carotenoids (the vitamin A precursor with antioxidant properties) were inversely associated with levels of depression in one study [56]. Vitamin C levels were not found to be associated with severity of depression in pregnant women [74], the elderly [28], or the general population [56]. Vitamin E has received more interest and two of six studies have found an inverse correlation between vitamin E levels and depressive symptoms [53, 55]. The Shibata [52] study did not find an association between vitamin E levels and depression at baseline, but serum vitamin E levels did predict depressive outcomes after four years.

Minerals

Twelve studies identified in this review have evaluated the relationship between iron levels and depression, and 10 of the 12 have demonstrated an inverse relationship between biomarkers of iron status and depressive symptoms. The two studies that did not demonstrate a significant inverse relationship were in populations of women who were pregnant [74] or had recently given birth [61]. Another sample of postpartum women did demonstrate a significant inverse relationship between iron status and severity of depression [60], and another found that poor iron status 48 hours post-partum was associated with an increased risk of developing post-partum depression (odds ratio=3.73, 95% CI: 1.84–7.56; P=0.0001 for ferritin cutoff value of 7.26 µg/L) [64]. Shariatpanaahi *et al.* [62] also found an association between low ferritin levels and depression in female medical students. The odds of reporting Beck Depression Inventory scores indicative of depression were increased by 1.92 for women with iron deficiency (classed as serum ferritin levels of 15 ng/L or less) compared to women with serum ferritin levels over 15 ng/L.

Zinc levels were studied in five articles, and all of these studies found serum and plasma zinc levels to be lower in patients with depression than in healthy controls. For example zinc levels were 22% lower for depressed patients versus healthy volunteers in the Siwek study [70], and correlated with severity of depression in other studies [68]. Despite consistent evidence associating low levels of zinc with depression, this evidence is based on small sample sizes (n < 100), all within Europe only, and four of five studies were conducted by the same group of authors [19, 67-69]. Copper levels were also measured in the 1997 Maes [68] study and not found to be associated with depression.

Smaller numbers of studies have investigated the relationships between magnesium, calcium, sodium and potassium levels with depression. Magnesium has been a nutrient of interest for supplementation studies, but only one [72] of the three studies identified for this review found an inverse relationship between serum magnesium levels and depressive symptoms. Although only considered in two studies presented here, calcium levels have been found to be consistently lower in patients with major depression [71, 72]. The evidence for calcium and magnesium is also based only on small case series or case-control studies. Sodium and potassium levels were measured in two small case-control studies [71, 72] and not found to be associated with depressive symptoms.

Strength of the Evidence

There is sufficient evidence to support an association between depression and blood nutrient levels of n-3 PUFAs, vitamin D, iron and zinc. There is limited support for an association between n-3 PUFA levels and depressive symptoms; the studies reported generally have small sample sizes, have limitations in their design, and there are studies presenting inconsistent results. There is fair evidence of an association between vitamin D levels and depressive symptoms; the level of evidence here was limited by the presence of two large studies [41, 46] that did not demonstrate an association. There is also fair evidence of an association between iron and depressive symptoms, also limited by small sample sizes and two studies reported here with inconsistent results. There was limited support for an association between blood levels of zinc and depression; while all studies reported here demonstrated an association, they were of small sample sizes and had limitations in their study designs.

DISCUSSION

The relationship between nutrient status and depression has been studied with many nutrients. In studies published over the past 20 years and identified in this review, there appears to be support for an

association between blood levels of n-3 PUFAs, vitamin D, iron and zinc with depression. Other nutrients of interest such as folate, vitamin B12, magnesium and antioxidants have had conflicting findings in the studies reviewed here. Due to the variety of experimental designs, measures of depression, nutrient biomarkers and statistical methods used, it is difficult to determine the strength of these associations.

It is also important to note several limitations encountered with the heterogeneous studies reviewed. The studies presented here used a variety of methods to measure nutrient status. Most studies described limitations of the measurements used, with the most frequently cited limitation being the use of only one type of sampling tissue. Biomarkers in some tissues will be more accurate than in others; however, the choice of sampling tissue may have been limited by cost and access to appropriate equipment for analysis. Some studies used specific cut-off points to identify participants with nutrient deficiency, while others simply noted associations between nutrient levels and depressive symptoms or diagnosis of depression. The definition of depression varied with some studies using diagnostic interviews based on the Diagnostic and Statistical Manual of Mental Disorders [3], and others using cut-off points on self-report scales. A range of treatments for depression were being used by participants in some studies, while in others a wash out period for any medication was provided prior to measuring nutrient status.

The sample population varied widely amongst studies with some studies using community dwelling participants and others using hospital inpatients. In some cases, the sample population was limited to a specific group such as adults over age 65 years, or pregnant women. Twenty-two of the 61 studies reviewed had sample populations of less than 100 individuals. Many of these studies, and even some of the larger ones, had sample populations composed primarily or completely of a specific ethnic background. For example, it was stated that all participants were Caucasian in the Maes[57] study on iron and depression. However, given that populations studied in the articles presented here are derived from North America, South America, Europe, Asia, Africa and Australia, it is possible that collectively, consistent results may be indicative of an association that is relevant to the global population.

Where an association has been demonstrated between nutrient levels and depression, it is usually not known whether low blood nutrient levels are related to nutrient intake. There are a number of factors that may impact on blood nutrient levels including dietary intake, intestinal absorption, nutrient loss or excretion, and immediate functional requirements. Some biomarkers, such as haemoglobin (a marker of iron status), will be reflective of longer term nutrient status and may indicate an increase in nutrient requirements or nutrient losses over several months. Dietary intake was not measured in most of the studies presented here. One study evaluating vitamin E levels found that the recommended intake was met or exceeded by 89% of participations, and that dietary intake was not related to plasma α –tocopherol level [55]. Thus, factors beyond dietary intake play a role in blood nutrient status.

Very few studies evaluating the association between nutrient levels and depression have been longitudinal, so it cannot be determined whether poor blood nutrient status leads to depressive symptoms, or whether depressive symptoms including poor appetite, amotivation and fatigue lead to altered dietary patterns which in turn impact on blood nutrient status. Five prospective cohort studies reviewed here have demonstrated that for some nutrients (in this case vitamin D [43], iron [60, 64], folate [37] and n-3 PUFA [20]), the low blood nutrient levels *precede* the development of depression. Even with a demonstrated directional relationship, it is not known whether the diminished blood nutrient status is related to dietary intake or other factors such as increased nutrient requirements.

The relationship between dietary intake and depression has been the focus of a number of other reviews [78, 79]. Like the data presented here, these reviews have generally found some evidence to suggest an association between nutrient intake and depression, with small or biased samples and inconsistent results limiting the generalisability of their findings. Cohort studies have also found that intakes of some foods and nutrients (including folate, n-3 PUFA, monounsaturated fats, olive oil, fish, fruit, vegetables, nuts and legumes, meat, poultry and game) are associated with a lower risk of developing depression [78, 80, 81]. More recently studies evaluating dietary patterns have demonstrated that traditional dietary patterns such as a Mediterranean diet are associated with a lower likelihood of developing depressive symptoms [82].

Given that depression is an illness that begins at a young age, is often recurring, and can have a

significant effect on functioning, there has been an increased focus on the prevention of depression [83, 84] with diet and other lifestyle factors identified as risk factors for depression [83]. At present, there are very few prospective cohort studies that have evaluated nutrient status, dietary intake and risk of depressive disorders. It is likely that consuming a traditional or healthy dietary pattern consistent with national dietary guidelines, and correcting nutrient deficiencies may both reduce the risk of developing depression. Further research is needed to elucidate whether the associations between nutrient status and depression are related to dietary intake. Randomised controlled trials investigating both nutrient supplementation and specific dietary patterns are needed to provide evidence to support dietary recommendations for the prevention of depressive disorders.

CONCLUSION

This review supports an association between blood levels of n-3 PUFAs, vitamin D, iron and zinc with depression. Due to the very small number of cohort studies and clinical trials evaluating the relationship between nutrient status and depression over time, a causal direction is yet to be established. It is likely that the relationship between blood nutrient levels and depression is bi-directional: nutrient deficiency can lead to depression, and depressive symptoms can impact on nutrient intake and lead to nutrient deficiency. There is significant scope for further research in this area. Both cohort studies that monitor the diet and mental health of large populations over time, and clinical trials of dietary interventions are warranted. Key components of dietary interventions include nutrients of interest such as n-3 PUFA, vitamin D, iron, and zinc, as well as a range of culturally appropriate 'healthy' dietary patterns. At this stage, prudent advice for individuals seeking to prevent or manage depressive symptoms would include correcting any nutrient deficiencies and adhering to national dietary guidelines.

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