

## The Correlation between Depression and Folate Deficiency

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### ABSTRACT

**Background:** Folate is a naturally occurring B vitamin, is needed in the brain for the synthesis of norepinephrine, serotonin, and dopamine. Thus, previous researches suggested that folate levels play an important role in the etiology and course of depression. However, the literature has been inconsistent regarding differences in folate level between individuals with and without depression. The present meta-analysis synthesized the results of previous studies to examine whether individuals with depression had lower levels of folate than individuals without depression.

**Aim of the Study:** to assess the relationship between Depression and Folate deficiency.

**Methods:** A review of the scientific literature (PubMed Search 1994 to 2017)

Pubmed, Embase and CENTRAL were searched to identify randomized controlled trials that investigated The Correlation between Depression and Folate Deficiency as the primary outcome. Identification of papers and data extraction was performed by two independent researchers.

We searched for relevant trials in the Cochrane Library, MEDLINE (from 1946), Embase (from 1974), the Transfusion Evidence Library (from 1980), and ongoing trial databases; all searches current to October 2017.

**Results:** 8 studies were included enrolling 173000 participants; 1813 patients with depression and 15487 control subjects. Pooling of all estimates showed a significant correlation between folate status and depression (OR pooled unadjusted=1.41; 95% CI 1.19 to 1.82), (OR pooled adjusted=1.39; 95% CI 1.04 to 1.76).

**Conclusion:** Low folate and B12 serum levels seem to be associated with depression Folate has been linked to depression and there is a strong body of evidence suggesting the introduction of folate supplement in the prevention and treatment of depression at the population and individual levels.

**Keywords:** folate, vitamin B12, depression, meta-analysis, gender, geriatric.

### INTRODUCTION

Depression has a major impact on public health . even though possible role of nutritional factors are involved in the pathogenesis of neuro - psychiatric disorders have been in question, some clinical studies have shown a significant relationship between folate status and depression<sup>(1)</sup>.

Folate plays a crucial role in the one-carbon metabolism for physiological nucleic acid synthesis and cell division, regulation of gene expression, amino acid metabolism and neurotransmitter synthesis<sup>(2)</sup>. Folate and vitamin B<sub>12</sub> are involved in the one-carbon metabolism

necessary for the production of monoamine transmitters. Several case-control studies since the 1960s have shown high prevalences of folate and vitamin B<sub>12</sub> deficiency in depression<sup>(3)</sup>. More recently, the total plasma homocysteine level was shown to be a sensitive marker of folate and vitamin B<sub>12</sub> deficiency, and higher concentrations of homocysteine were observed in depressed patients<sup>(4)</sup>.

Both low folate and low vitamin B12 status have been found in studies of depressive patients, and an association between depression and low levels of the two vitamins is found in studies of the general population. Low plasma or serum folate has also been found in patients with recurrent

mood disorders treated by lithium. A link between depression and low folate has similarly been found in patients with alcoholism. It is interesting to note that Hong Kong and Taiwan populations with traditional Chinese diets (rich in folate), including patients with major depression, have high serum folate concentrations. However, these countries have very low life time rates of major depression. Low folate levels are further more linked to a poor response to antidepressants, and treatment with folic acid was shown to improve response to antidepressants<sup>(5)</sup>.

Studies vary depending on the criteria used to define folate deficiency, but often, about one-third of depression patients were deficient in folate . Given that depression is often accompanied by decreased appetite and weight loss, the high incidence of folate deficiency in depression patients is not surprising. However, there is some evidence, though not conclusive, that folate deficiency may be involved in the etiology of depression in a minority of patients. Alternatively, depressed mood may decrease appetite, lower folate levels and thereby help to prevent recovery from depression. A recent review and meta analysis looked at the results from the limited number of studies that investigated the effect of giving folate to depression patients and concluded that “there is some evidence that augmentation of antidepressant treatment with folate may improve patient outcome<sup>(6)</sup>, however it is not clear whether the beneficial effect of folate is limited to only patients with folate deficiency<sup>(6)</sup>.

## MATERIALS AND METHODS

This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, systematically identifying and appraising peer-reviewed RCTs reporting on the effect of Folate supplementation for individuals with symptoms of depression with the objectives of investigating:

- The primary evidence for Folate supplementation and depression from RCTs
- The types of subjects
- The dose of Folate supplementation
- The control interventions the measures of outcome used
- Methodological quality of the studies
- Estimates of the size of the effect.

## Search Approach

A systematic search for relevant RCTs was performed evaluating oral Folate supplementation that included data on depression using four library databases of PsychINFO, MedLine, PubMed and Cochrane online library. Search approaches for the different databases can be obtained from the researchers. All databases were searched from inception to October 2017, with eligible papers limited to English language and human subjects.

## Eligible Studies

### Inclusion Criteria

1. Publications in English and Arabic languages.
2. Prospective, retrospective cohort and cross-sectional, case-control studies.
3. Inclusion of Control groups.
4. Studies must be comparing between the presence of low folate status and depression.

### Exclusion Criteria

Studies of different endpoint or selected languages (English and Arabic). Studies were not excluded on their methodological quality as the entire evidence base was required to address the aims of this research.

### Decision-Making

Relevant publications were identified according to the title, abstract and study descriptors by one researcher; the decision to include the article was independently validated by a second and disagreements were referred to third for an independent ruling.

### Critical Appraisal

Methodological quality of articles was critically appraised with PEDro<sup>(7)</sup>. Trials were rated with a checklist, the PEDro scale. This considers two aspects of trial quality; internal validity of the trial and whether the trial contains sufficient statistical information to make it interpretable. It does not rate external validity or the effect size.

### Data Extraction

Summary odds ratios (ORs) and group mean folate levels, with attendant 95% CIs, were extracted or calculated from original data. Both unadjusted and adjusted summary ORs were sought, where authors had provided these items.

**Independence**

Independent researchers investigated the library databases to reduce errors/bias in accessing evidence.

**Meta-Analysis**

Random effects meta-analysis was used <sup>(8)</sup>. Differences in mean folate levels between people who and were and were not depressed were pooled using a standardized effect of sample size<sup>(9)</sup>. We chose this method to allow both mean serum and red cell folate, measured with a variety of different assay techniques, to be combined across studies.

P-Values for meta-regression were calculated using 1000 Monte-Carlo simulations, with a permutation test to avoid potential false positives<sup>(10)</sup>.

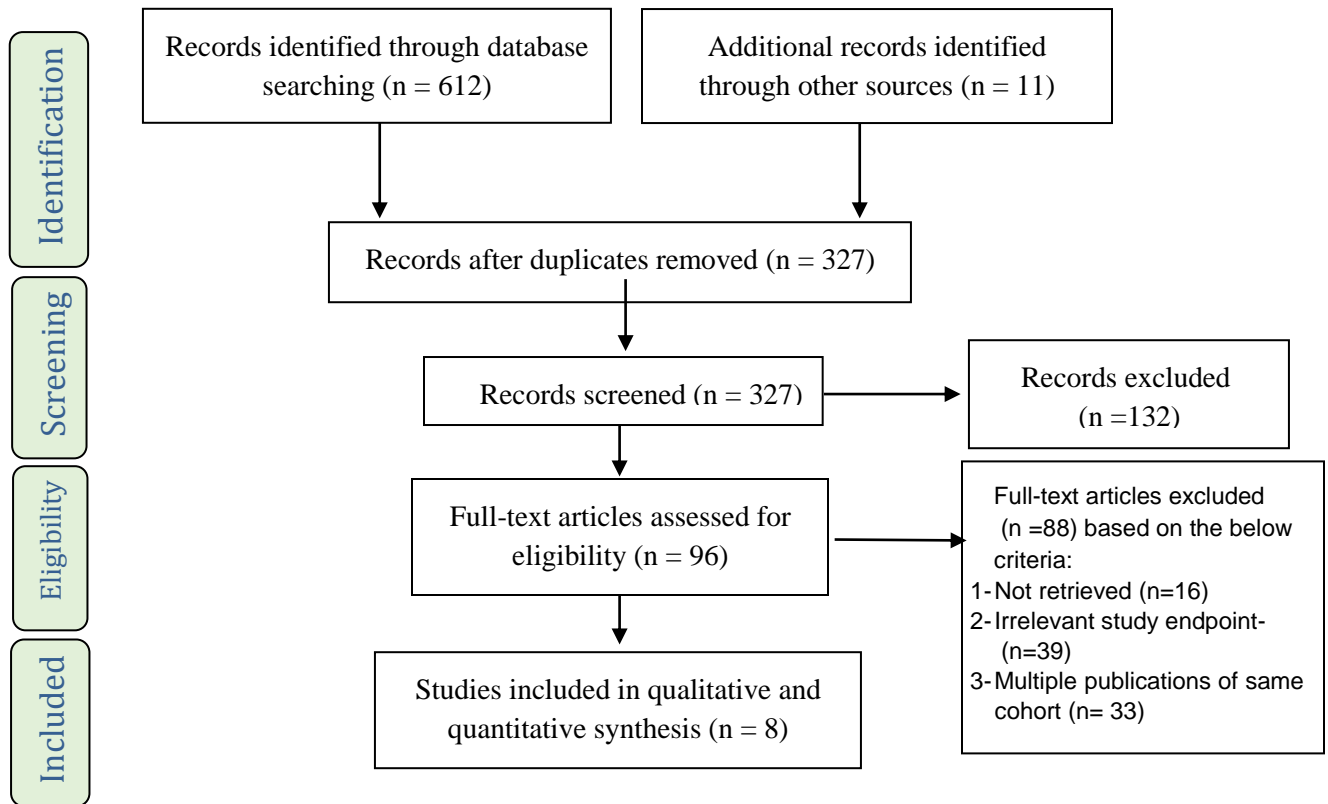
**RESULTS**

The initial search was comprehensive, we accepted all article related to Folate correlation and supplementation impact on depression to ensure a

comprehensive view of available work, and generated 612 articles. Preliminary application of study criteria identified 327 potential studies for inclusion that met one or more criteria. Further review of these investigations by independent reviewers yielded 96 RCTs that fully met all inclusion criteria.

No individual authors were contacted for information. No further review of methodological quality of the studies was conducted beyond that it appeared in a peer review journal and comprised an RCT. The 96 eligible articles were again closely examined and data extracted using a standard protocol regarding target population, sample size, program provider, program content, intervention components, processes, and outcomes. Comparison among provider type was computation of differences between percent of successful program to number attempted. No further statistical analyses were employed.

Finally, 8 studies were included and detailed as the focus for the present study.



**Figure 1: PRISMA flow diagram showing the selection criteria of the assessed studies <sup>(11)</sup>.**

**Low folate level correlation with depression**

Overall all, 8 studies included 17300 participants-1813 were diagnosed with depression and 15487 served as Controls- examined the correlation between low folate level and depression as variables, and provided sufficient data to calculate ORs (table 1 and Table 2). Seven of these were cross-sectional studies<sup>(12-16, 18-19)</sup> in which folate status and depression were ascertained simultaneously from population surveys and the proportion of patients with depression with low folate status was compared to that of patients who suffered no depression with low folate status.

Cross-sectional studies were often drawn from large population-based cohort studies examining the correlation between the physical and nutritional variables and health outcomes—One example, one large cross-sectional study conducted by pennix *et al*<sup>(12)</sup> was drawn from the Women's Health and Ageing studies<sup>(20)</sup>. Amongst these population surveys, depression status was ascertained either by standardized interview or by scores on a standardized psychometric instrument, such as the Geriatric Depression Scale, in the case of the Women's Health and Ageing study.

**Table 1: Baseline characteristics of the included study**

Study	Year of Study	Study Design	Participants	Description of the case	Controls	Folate level
Pennix <i>et al.</i> <sup>(12)</sup>	2000	Cross-sectional survey	Women ≥65 years from a Population survey	Severe depression on the GDS score ≥14 (n=122)	Non-depressed people from the same population, GDS score ≤9 (n=478)	Serum folate <5.03 ng/ml <11.4 nmol/l and raised homocysteine (>13.9 nmol)
Lindeman <sup>(13)</sup>	2000	Cross-sectional survey	Hispanic males and females aged ≥65 years	GDS score >6 (n=74)	Not currently depressed and from the same population (n=709)	Serum folate <5 ng/ml <11.1 nmol/l
Tiemeier <i>et al.</i> <sup>(14)</sup>	2002	Cross-sectional survey	Patients >55 years from a population survey	DSM-IV depression or dysthymia (n=112)	Randomly selected non-depressed people from the same population (n=416)	Serum folate <5.03 ng/ml <11.4 nmol/l + raised homocysteine (>13.9 nmol/L)
Bjelland <i>et al.</i> <sup>(15)</sup>	2003	Cross-sectional survey	Men and women aged 46–49 and 70–74 years from a population cohort study	High score on HAD >8 (n=243)	Non-depressed people from the same population (n=5705)	Serum folate <1.68 ng/ml <3.8 nmol/l
Tolmunen <i>et al.</i> <sup>(16)</sup>	2003	Cross-sectional survey	Middle-aged Finnish men 42–60 years from a population cohort	High score on HPL scale ≥5 (n=228)	Non-depressed people from the same population (n=2215)	Ascertained from dietary records. Lowest third tertile of folate intake (daily intake <201.9 (SD 52) µg/day)
Tolmunen <i>et al.</i> <sup>(17)</sup>	2004	Cohort study	Middle-aged Finnish men 42–60 years from population cohort	Hospital discharge diagnosis of ICD major depression during 15-year follow-up (n=47)	No ICD diagnosis of depression during 15-year follow-up (n=2313)	Ascertained from dietary records. Below median folate intake (256 µg/day)
Ramos <i>et al.</i> <sup>(18)</sup>	2004	Cross-sectional study	Elderly Latino males (n=627) and females	CES-D score >15 (n=385)	Depression score ≤15 from the same population	Serum folate in lowest tertile* <11.2 ng/ml

			(n=883) aged ≥60 years		(n=1125)	<25.4 nmol/l Study conducted post-fortification
Morris <i>et al.</i> (19)	2003	Cross-sectional study	Males and females aged 15– 39 years from a US National Population Nutrition Survey	Lifetime risk of DSM-III major depression (n=301) and dysthymia (n=121) ascertained by diagnostic interview (total n=422)	Ethnically diverse members from the same population (n=2526)	Red cell folate below 25th centile in the population* Cut-off provided by author <196 ng/ml<445 nmol/l

GDS: Geriatric Depression Scale; HAD, Hospital Anxiety and Depression, HPL: Human Population Laboratory; ICD: International Classification of Diseases; NA: not applicable; SES: socioeconomic status.

**Table 2: the relationship between folate status and risk of depression.**

Study	Year of Study	Measures	Adjusted OR (>1=association)	Unadjusted OR (>1=association)
Pennix <i>et al.</i> (12)	2000	Age, race education; income; BMI serum creatinine; CCF; diabetes; disability; cancer	OR 0.90 (95% CI 0.24 to 3.36)	OR 0.78 (95% CI 0.22 to 2.73)
Lindeman <sup>(13)</sup>	2000	None	NA	OR 1.51(95% CI 0.82 to 2.71 )
Tiemeier <i>et al.</i> (14)	2002	Age, gender, education, smoking, alcohol intake, cognitive functioning	OR 1.49 (95% CI 0.83 to 2.67)	OR 1.52 (95% CI 0.85 to 2.71)
Bjelland <i>et al.</i> (15)	2003	Age, sex, smoking status, educational level	OR 1.31 (95% CI 0.82 to 2.11)	OR 1.48 (95% CI 0.93 to 2.37)
Tolmunen <i>et al.</i> (16)	2003	Age, sex, smoking, alcohol, appetite, BMI, living alone, education, SES, fat consumption	OR 1.46 (1.01 to 2.12)	OR 1.67 (95% CI 1.19 to 2.35) *Least-adjusted for age and examination years
Tolmunen <i>et al.</i> (17)	2004	Age and examination year, SES, baseline depression score, daily intake of fibre, vitamin C and fat	OR 2.53 (95% CI 1.17 to 5.48)	OR 3.04 (95% CI 1.58 to 5.86)
Ramos <i>et al.</i> (18)	2004	Age, education, B12 status, homocysteine levels, use of folate supplements, use of anti-depressants and alcohol consumption	Overall OR 75 (95% CI 0.42 to 1.33) Men OR 0.74 (95% CI 0.40 to 1.35) Women OR 2.04 (95% CI 1.38 to 3.02)	Overall OR 0.96 (95% CI 0.56 to 1.65) Men OR 0.96 (95% CI 0.56 to 1.65) Folate*sex interaction, so analysis also presented separately for men and women. Women OR 2.08 (95% CI 1.47 to 2.95)
Morris <i>et al.</i> (19)	2003	Gender age, race, income, education, alcohol use, drug use, weight and nutritional status	OR 2.4 (95% CI 1.3 to 4.4)	OR 1.7 (95% CI 1.1 to 2.6) †Least adjusted—adjusts only for age, sex and ethnicity Based upon unpublished data from author.

BMI: body mass index; CCF: congestive cardiac failure, CES-D: Center for Epidemiologic Studies—Depression, DSM: Diagnostic and Statistical Manual for mental disorders.

**Folate status and depression meta-analysis**

Sufficient data were available from the 8 studies to allow statistical pooling of the estimates of the relationship between categorical folate status and depression (**Table 3**).

Thus, this meta-analysis included data from 173000 participants—1813 with depression and 15487 control subjects. Pooling of all estimates showed a significant correlation between folate status and depression (OR<sub>pooled unadjusted</sub>=1.41; 95% CI 1.19 to 1.82), (OR<sub>pooled adjusted</sub>=1.39; 95% CI 1.04 to 1.76)

**Table 3:** Overall meta-analysis Outcome of the included studies:

Meta-analysis Outcome	Odds ratio (95% CI)
Unadjusted	1.41 (1.19- 1.82)
Adjusted	1.39(1.04 to 1.76)
Standardized mean differences	Plasma folate=> 0.15 (0.08, 0.23) Red cell folate => 0.35 (0.07-0.63)

**Unadjusted/adjusted:** refers to adjustment for potential confounding:

**DISCUSSION**

There has been a compelling need to address the relationship between folate and depression, the most pressing of which is larger studies on the ability of folate to potentiate the action of standard antidepressant and pharmacological therapies. Additional issues are needed to be addressed and the exact dosage of folate required to maximize its response may differ in different subgroups, especially for those with and without overt folate deficiency.

Moreover, questions like, should depressed patients received folate supplements, and how much was the dose? Is there is no need for additional supplements in countries with mandatory or with voluntary fortification of foods with folate? The appropriate dose of folate needed to help regulate mood, depends on serum or red blood cell levels, is not clear and this topic needs further investigations. Therefore, In the present systematic review and meta-analysis we dedicated our research and efforts to identify the relationship between Folate status and depression.

Nevertheless, the majority of the studies included provided epidemiologically weaker cross-sectional and case–control studies that demonstrate only association, which may still be driven by causality. Some preliminary evidences of a direction of causality comes from the single-cohort study carried by Tolmunen *et al.*<sup>(17)</sup> in which folate was determined prior to the onset of depression, reducing the possibility of a reverse causal relationship<sup>(21)</sup>. Obviously, this result requires replication using an extended population to begin to draw inference about the direction of causality between low folate and depression.

In contrast, Pennix *et al.*<sup>(12)</sup> reported that physically disabled women with vitamin B<sub>12</sub> deficiency were twice as likely to have severe depressive symptoms. However, they observed no association between homocysteine or folate and depression.

The results of the present review should be considered in conjunction with emerging evidence of an attribution of impairments in folate metabolism with depression<sup>(22)</sup>.

The evidence of folate being a causal factor in depression is supported by an evolving association between the common polymorphism of a gene involved in the metabolism of folate which is methylene tetrahydrofolate reductase (MTHFR), and depression<sup>(23)</sup>. The specific polymorphism *MTHFR* C677T has been found to be associated with depression in several studies<sup>(15,24,25)</sup>.and has now been confirmed using meta-analysis<sup>(22)</sup>. The *MTHFR* C677T polymorphism mimics low folate status, but is not susceptible to either confounding or reverse causality. The association between depression and being homozygous for the *MTHFR* C677T polymorphism in genetic studies is of a similar magnitude (OR=1.36) to that demonstrated in our least confounded pooled estimate in the present study. This is an example of what has been termed Mendelian randomisation and provides further circumstantial and complementary evidence of a potentially causal link between low folate status and depression<sup>(26)</sup>.

**CONCLUSION**

There are growing body of evidences that Folate has been causatively wired to depression . thus , folate supplement can in turn contribute in the prevention and treatment of depression at the population and individual levels.

The association is largely based on large cross-sectional studies and is confirmed in only one prospective cohort study. Nevertheless, the possibility of reverse causality should not be excluded.

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