BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

In adults with depression and low mood, how effective is folic acid, compared to any other pharmacological intervention, in improving mood?

Clarification of question using *PICO* structure

Patients: Adults with depression and low mood
Intervention: Folic acid
Comparator: Any other pharmacological intervention
Outcome: Improving mood

Plain language summary

There is minimal evidence available to determine whether folic acid can help with depression and low mood and there are no clinical guidelines available. More research is needed to help understand this area further.

Email: awp.BESTinMH@nhs.net Phone: 0117 378 4232/4233/4335 @BESTinMH

Clinical and research implications

No definite clinical implications may be made based on the evidence included in this BEST summary. There were no studies that directly compared folic acid with any other pharmacological interventions in adults with depression, with the exception of one RCT included in a Cochrane review. This RCT compared folate with trazodone in patients with comorbid *dementia and depression*, so that it's applicability to this BEST summary is questionable.

A Cochrane review published in 2003 suggested that 'the available evidence raises the possibility that folate may have therapeutic potential as an *augmentation* strategy in the treatment of depressive disorder' but that 'further randomised trials are required to establish the exact magnitude of the main effect'. One such subsequent trial was the FolATED trial (included in this BEST summary). This trial was large and well-conducted, and there is convincing evidence from this study to suggest that folic acid is not an effective adjunct to antidepressant therapy. As such, the authors suggested that their findings 'demand reappraisal of this consensus and associated treatment guidelines.' They also make a case for future research to investigate the use of 5-MTHF.

Most of the study authors suggested that further research is needed – to evaluate the effectiveness of the various strategies in a wider population group, or in groups with different folate levels.

What does the evidence say?

Number of included studies/reviews (number of participants)

One systematic review (SR) (Taylor et al. 2003) and four randomised controlled trials (RCTs) (Almeida et al. 2014; Başoğlu et al. 2008; Bedson et al. 2014; Resler et al. 2008) met the inclusion criteria for this BEST summary. We note, however, that all of the included RCTs evaluated folic acid *augmentation* (i.e. folic acid plus an antidepressant) compared with an antidepressant plus a placebo, rather than comparing folic acid vs. any other pharmacological intervention *per se*. Only one trial included in the SR above examined the use of folate as an alternative to conventional antidepressant therapy (Passeri 1991).

Main findings

The SR by Taylor et al. (2003) aimed to assess the effectiveness of folate in the treatment of depression. This review included 3 RCTs (n=151), two of which compared folate with placebo in the context of continued use of other psychotropic medication, and one (n=96) which compared folate with trazodone. HDRS scores were significantly improved (i.e. reduced) in favour of folate when data were pooled from the first two of these three studies (WMD-2.65; 95% CI -4.93 to -0.38), although the confidence intervals were wide. When folate was compared with trazodone for patients with comorbid dementia and depression, no significant difference was found for the HDRS. One study that compared folate with placebo also reported a clinician-rated outcome scale combining symptom resolution and social functioning. Using this scale, the results favoured treatment with folate, WMD -0.90 (95% CI -1.45 to -0.35) (n=24).

The RCT by Almeida et al. (2014) compared **citalopram** plus vitamins B6, B12 and folic acid, with citalopram plus placebo, in 153 adults aged 50 years or over with DSM-IV-TR major depression. The

authors found that more patients who received the adjunctive use of folic acid, vitamin B6 and vitamin B12 experienced remission over 52 weeks than those who received placebo (OR 2.49; 95% CI 1.12 to 5.51), but not over the initial 12 weeks. There were no significant differences between the groups, however, in the proportion of patients with reduced MADRS scores.

Başoğlu et al. (2008) compared **escitalopram** plus folic acid, with escitalopram only, in 42 people (35 included in the analysis) with major depressive disorder. In this trial, a higher percentage of patients showed response in those who received only escitalopram compared to those who received adjuvant folic acid supplementation at 6 weeks (80% vs. 35%, p=0.016). Patients who received adjuvant folic acid supplementation, however, had significantly higher MADRS scores (p=0.013), but there were no significant differences in CGI scores between the groups.

The FolATED trial, conducted by Bedson et al. (2014), compared 12 weeks **antidepressant medication** (ADM) (as prescribed to each patient) plus folic acid, with ADM plus placebo, in 475 adults with moderate or severe depression. At various time-points up to 25 weeks follow-up, the addition of folic acid did not significantly improve 12 out of 13 main outcomes – BDI-II (primary), MADRS, CGI (three scales), EQ-5D (two scores), SF-12 (two scales) and UKU (four scales). The only significant result (SF-12 Mental Component Score) was in favour of the ADM plus placebo group (p=0.017).

Resler et al. (2008) compared **fluoxetine** plus folic acid, with fluoxetine plus placebo, in 27 adults diagnosed with a major depressive episode. After 6 weeks, the average HDRS score was significantly improved in the folate group compared with the placebo group (p = 0.04). No other mood outcomes were evaluated in this trial.

Authors conclusions

The Cochrane review by Taylor et al. (2003) and colleagues concluded that "the currently available evidence suggests that folate supplementation may be effective when used in addition to conventional antidepressant medication. The evidence does not support the use of folate as a replacement for antidepressant medication in the treatment of depression."

Almeida et al. (2014) concluded that "B-vitamins did not increase the 12-week efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over one year in middle-aged and older adults with major depression."

Başoğlu et al. (2008) concluded that "…while escitalopram is an effective antidepresssant in major depressive patients, adjuvant treatment with folic acid was not found to have an enhancing impact antidepressant efficacy."

Bedson et al. (2014) concluded that there was no evidence to suggest that that folic acid was clinically effective.

Resler et al. (2008) did not make any conclusions relating to HDRS scores, but suggested that

co-administration of folate in antidepressant treatment may be of increasing interest (based on results from plasma folate, homocysteine and vitamin B 12, and serotonin concentration in lymphocytes).

Reliability of conclusions/Strength of evidence
The SR by Taylor et al. (2003) had a low risk of bias, but given the number of relevant studies published after 2003, the results from this review are not up to date.

The RCTs by Almeida et al. (2014) and Bedson et al. (2014) had a low risk of bias, so that their results, and the conclusions based on them, are likely to be reliable. Başoğlu et al. (2008) had a high risk of bias, so that the reliability of their study results are uncertain. Due to a lack of methodological reporting, Resler et al. (2008) had an unclear risk of bias.

What do guidelines say?

NICE guidelines do not comment on the use of folic acid to treat depression and/or low mood.

Date question received: 23/02/2016
Date searches conducted: 08/03/2016
Date answer completed: 08/04/2016

References

Systematic reviews

Taylor MJ, Carney SM, Geddes J, Goodwin G. Folate for depressive disorders. *Cochrane Database of Systematic Reviews* 2003

Randomised controlled trials

Almeida, O. P., Ford, A. H., Hirani, V., Singh, V., McCaul, K., & Flicker, L. (2014). B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomised, double-blind, placebo-controlled trial. *The British Journal of Psychiatry*, *205*(6), 450-457.

Başoğlu, C., Ateş, M. A., Algül, A., İpçioğlu, O. M., Geçici, Ö., Yılmaz, O., & Kılıç, S. (2009). Adjuvant folate with escitalopram treatment and homocystein, folate, vitamin B-12 levels in patients with major depressive disorder. *KLINIK PSIKOFARMAKOLOJI BULTENI-BULLETIN OF CLINICAL PSYCHOPHARMACOLOGY*, *19*(2), 135-142.

Bedson, E., Bell, D., Carr, D., Carter, B., Hughes, D., Jorgensen, A. & Pink, J. (2014). Folate Augmentation of Treatment–Evaluation for Depression (FolATED): randomised trial and economic evaluation.

Resler, G., Lavie, R., Campos, J., Mata, S., Urbina, M., García, A., & Lima, L. (2008). Effect of folic acid combined with fluoxetine in patients with major depression on plasma homocysteine and vitamin B12, and serotonin levels in lymphocytes. *Neuroimmunomodulation*, *15*(3), 145-152.

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Taylor et al. (2003)	Updated searched 12/5/2005	***Participants***: All patients suffering from depressive disorder diagnoses according to explicit criteria, including major depressive disorder, bipolar affective disorder and dysthymic disorder. ***Intervention***: Folic acid ***Comparator***: Placebo or other antidepressant medication in the treatment of depressive disorder. ***Outcome***: Resolution of depressive episode, quality of life, hospital admission, social functioning and occupational functioning. ***Study design*****:** RCTs were eligible for inclusion.	3 RCTs (n=247)	Two studies (n=151) compared treatment of **folate with placebo** in the context of continued use of other psychotropic medication. Pooling the HDRS score favoured treatment with folate (WMD -2.65; 95% CI -4.93 to -0.38; I^2=0%). The SR authors also reported that' fewer patients treated with folate experienced a reduction in their HDRS score of less than 50% at ten weeks' (RR 0.47 [95% CI 0.24 to 0.92]) (1 trial, n=100). One study comparing folate with placebo also reported a clinician-rated outcome scale combining symptom resolution and social functioning. On this scale, the results favoured treatment with folate, WMD -0.90 (95% CI -1.45 to -0.35) (n=24). When **folate was compared with trazodone**	Low

				for patients with comorbid dementia and depression, no significant difference was found for the HDRS (WMD was -1.00 [95% CI -3.21 to 1.21]) (1 trial, n=96). Treatment with folate was no more likely to avoid a reduction in HDRS of less than 50% (RR 0.97, 95% CI 0.84 to 1.12).	

Randomised controlled trials

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Almeida et al. (2014)	***Participants*****:** Adults (50 years and over) in the community with major depression according to DSM-IV-TR. ***Intervention*****:** Citalopram with folic acid 2mg, vitamin B6 45mg and B12 0.5mg for 52 weeks. ***Comparator*****:** Citalopram plus placebo. ***Outcome*****:** Symptom severity (MADRS).	N=153 (vitamin arm n=77, placebo arm n=76)	The authors reported that more people treated with vitamins than placebo experienced remission over 52 weeks (OR = 2.49, 95% CI=1.12, 5.51, after adjustment for gender and baseline tHcy). There was no evidence that adjunctive treatment with vitamins was associated with faster or more pronounced reduction of MADRS scores (≥50%) over 12 and 52 weeks (52 weeks: OR = 0.59, 95% CI=0.28, 1.25). However, amongst those who were no longer depressed by week 12, relapse of symptoms at 26 and 52 weeks was less frequent among participants assigned vitamins than placebo (OR = 0.33, 95% CI=0.12, 0.94). There were no significant differences between the groups for	Low

			any adverse event.	
Başoğlu et al. (2009)	***Participants*:** Patients with major depressive disorder according to DSM-IV who were consecutively admitted to an outpatient psychiatric unit. ***Intervention*:** 10mg escitalopram and 2.5mg folic acid. ***Comparator*:** 10mg escitalopram only. ***Outcome*:** Symptom severity (MADRS and CGI).	N=42 (n= 35 analysed: folic acid arm n=20, escitalopram only arm n=15)	Patients receiving escitalopram (12/15; 80%) had a better response to treatment than the patients receiving escitalopram plus folic acid (7/20; 35%) (P=0.016) at 6 weeks. There was a significant difference in MADRS scores between the groups at 6 weeks in favour of adjunctive treatment: median 12 (range 6 to 35) in escitalopram group vs. median 16 (10 to 33) in escitalopram plus folic acid group (p=0.013), but there was no significant difference between groups in CGI: median 2 (range 1 to 4) in escitalopram group vs. median 2 (1 to 4) in escitalopram plus folic acid group.	High
Bedson et al. (2014)	***Participants*:** Adults (aged 18 and over) presenting to primary or secondary care with confirmed moderate to severe depression, about to start antidepressant medication. ***Intervention*:** 5mg folic acid added to antidepressant medication daily for 12 weeks. ***Comparator*:** Antidepressant medication plus placebo. ***Outcome*:** Symptom severity (BDI-II, CGI, MADRS, MINI), general health (SF-12, EQ-5D)	N=475 (237 to folic acid and 238 to placebo) (n=440 analysed)	At various time points up to 25 weeks follow-up, the addition of folic acid did not significantly improve 12 out of 13 main outcomes – BDI-II (primary), MADRS, CGI (three scales), EQ-5D (two scores), SF-12 (two scales) and UKU (four scales). The only significant result favoured the placebo in the SF-12 Mental Component Score (mean 31.99 (SD 9.34) in folate group vs. mean 34.09 (9.01) in placebo group, p=0.017). There were no significant differences between the groups in adverse events.	Low
Resler et al. (2008)	***Participants*:** Adults recently diagnoses with a major depressive episode not currently on antidepressant medication. ***Intervention*:** 20mg fluoxetine and 10 mg	N=27 (20 analysed)	After 6 weeks, the average HDRS score was significantly improved in the folate group (7.43 ± 1.65) compared with the placebo group (11.43 ± 1.31) (p = 0.04).	Unclear

	folic acid for 6 weeks. ***Comparator*:** Fluoxetine and placebo for 6 weeks. ***Outcome*:** Symptom severity (HDRS)			

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Taylor et al. (2003)	☺	☺	☺	☺	☺

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Almeida et al. (2014)	☺	☺	☺	☺	☺	?
Başoğlu et al. (2009)	☺	?	☹	?	☹	?
Bedson et al. (2014)	☺	☺	☺	☺	☺	☺
Resler et al. (2008)	☺	?	?	?	?	?

☺Low risk ☹High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
Guidelines			
NICE	Folic Acid Depression	117	0
Systematic Reviews			
MEDLINE	1 exp Folic Acid/ (32714) 2 (folic adj2 acid).ab,ti. (15872) 3 folate.ab,ti. (21018) 4 (vitamin* adj2 B9).ab,ti. (105) 5 (B adj2 vitamin*).ab,ti. (10517) 6 1 or 2 or 3 or 4 or 5 (53842) 7 exp Depression/ (85999) 8 exp Depressive Disorder/ (89303) 9 depress*.ab,ti. (347359) 10 (depress* adj3 disorder*).ab,ti. (37586) 11 (low adj2 mood).ab,ti. (586) 12 7 or 8 or 9 or 10 or 11 (386125) 13 6 and 12 (951) 14 (systematic$ review$ or meta-analytic$ or metanalysis or metaanalysis or meta analysis or meta?synthesis or meta synthesis or meta?regression or meta regression).ab,ti. (130945) 15 ((synthes$ adj3 (literature or evidence)) or integrative review or data synthesis or research synthesis or narrative synthesis or systematic study or systematic studies or systematic comparison$ or systematic overview$ or evidence based review or comprehensive review or critical review or quantitative review or structured review or realist review or realist synthesis).ab,ti. (50112) 16 exp Meta-Analysis/ (62191) 17 meta-analysis.ab,ti,pt. (92151)	117	

	18 14 or 15 or 16 or 17 (185971) 19 (medline or pubmed or Cochrane or embase or cinahl or psyc?lit or psyc?info).ab. (114715) 20 ((literature adj3 search$) or (database$ adj3 search$) or (bibliographic adj3 search$) or (electronic adj3 search$) or (electronic adj3 database$) or (computeri?ed adj3 search$) or (internet adj3 search$) or included studies or (inclusion adj3 studies) or inclusion criteria or selection criteria or predefined criteria or predetermined criteria).ab. (135072) 21 ((assess$ adj3 (quality or validity)) or (select$ adj3 (study or studies)) or (data adj3 extract$) or extracted data or (data adj2 abstracted) or (data adj3 abstraction) or published intervention$ or ((study or studies) adj2 evaluat$) or (intervention$ adj2 evaluat$) or confidence interval$ or heterogeneity or pooled or pooling or odds ratio$ or Jadad or coding).ab. (820045) 22 19 or 20 or 21 (943367) 23 review.pt. (2073060) 24 22 and 23 (146004) 25 22 and 23 (146004) 26 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ab,ti. (121644) 27 18 or 22 or 24 or 25 (1022323) 28 (letter or editorial or comment).pt. (1460743) 29 27 not 28 (1014446) 30 Animals/ (5779289) 31 Humans/ (15700913) 32 30 not 31 (4162343) 33 29 not 32 (924853) 34 13 and 33 (117)		
EMBASE	1 exp folic acid/ (49072) 2 (folic adj2 acid).ab,ti. (20341) 3 folate.ab,ti. (26453) 4 (vitamin adj2 B9).ab,ti. (133) 5 (B adj vitamin*).ab,ti. (2958) 6 1 or 2 or 3 or 4 or 5 (61605) 7 exp depression/ or exp major depression/ (358455) 8 depress*.ab,ti. (461215)	235	

	9 (depress* adj3 disorder*).ab,ti. (53468) 10 (low adj2 mood).ab,ti. (901) 11 7 or 8 or 9 or 10 (590912) 12 6 and 11 (1937) 13 (systematic$ review$ or systematic$ literature review$ or meta-analytic$ or meta?analysis or metanalysis or meta analysis or meta?synthesis or meta synthesis or meta?regression or meta regression).ab,ti. (171379) 14 ((synthes$ adj3 literature) or (synthes$ adj3 evidence) or (synthes$ adj2 qualitative) or integrative review or data synthesis or research synthesis or narrative synthesis or systematic study or systematic studies or systematic comparison$ or systematic overview$).ab,ti. (32232) 15 ((systematic adj2 search$) or systematic$ literature research$ or (review adj3 scientific literature) or (literature review adj2 side effect$) or (literature review adj2 adverse effect$) or (literature review adj2 adverse event$) or (evidence-based adj2 review) or (evidence-based adj2 review)).ab,ti. (19252) 16 (comprehensive review or critical review or critical analysis or quantitative review or structured review or realist review or realist synthesis or (pooled adj2 analysis) or (pooled data adj6 (studies or trials)) or (medline and (inclusion adj3 criteria)) or (search adj (strateg$ or term$))).ab,ti. (77815) 17 exp "systematic review"/ (102548) 18 meta analysis/ (105021) 19 (Medline or pubmed or Cochrane or embase or cinahl or psyc?lit or psyc?info or lilacs or (literature adj3 search$) or (database$ adj3 search$) or (bibliographic adj3 search$) or (electronic adj3 search$) or (electronic adj3 database$) or (computeri?ed adj3 search$) or (internet adj3 search$)).ab. (195210) 20 ((inclusion adj3 studies) or inclusion criteria or selection criteria or predefined criteria or predetermined criteria or (assess$ adj3 (quality or validity)) or (select$ adj3 (study or studies)) or (data adj3 extract$) or extracted data or (data adj2 abstracted)).ab. (236680) 21 ((data adj3 abstraction) or published intervention$ or ((study or studies) adj2 evaluat$) or (intervention$ adj2 evaluat$) or confidence interval$ or heterogeneity or pooled or pooling or odds ratio$ or (Jadad or coding) or evidence-based).ab. (975828) 22 13 or 14 or 15 or 16 or 17 or 18 (302486) 23 19 or 20 or 21 (1263196) 24 review.pt. (2135066) 25 23 and 24 (153652)		

	26 review.ti. (361497) 27 23 and 26 (80800) 28 (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ab,ti. (356094) 29 (retriev$ adj10 (papers or trials or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ab,ti. (17772) 30 22 or 25 or 27 or 28 or 29 (643095) 31 (letter or editorial).pt. (1428373) 32 30 not 31 (634790) 33 [limit 30 to yr="2010"] (0) 34 (systematic$ review$ or systematic$ literature review$ or meta-analytic$ or meta?analysis or metanalysis or meta analysis or meta?synthesis or meta synthesis or meta?regression or meta regression).ab,ti. (171379) 35 ((synthes$ adj3 literature) or (synthes$ adj3 evidence) or (synthes$ adj2 qualitative) or integrative review or data synthesis or research synthesis or narrative synthesis or systematic study or systematic studies or systematic comparison$ or systematic overview$).ab,ti. (32232) 36 ((systematic adj2 search$) or systematic$ literature research$ or (review adj3 scientific literature) or (literature review adj2 side effect$) or (literature review adj2 adverse effect$) or (literature review adj2 adverse event$) or (evidence-based adj2 review) or (evidence-based adj2 review)).ab,ti. (19252) 37 (comprehensive review or critical review or critical analysis or quantitative review or structured review or realist review or realist synthesis or (pooled adj2 analysis) or (pooled data adj6 (studies or trials)) or (medline and (inclusion adj3 criteria)) or (search adj (strateg$ or term$))).ab,ti. (77815) 38 exp "systematic review"/ (102548) 39 meta analysis/ (105021) 40 (Medline or pubmed or Cochrane or embase or cinahl or psyc?lit or psyc?info or lilacs or (literature adj3 search$) or (database$ adj3 search$) or (bibliographic adj3 search$) or (electronic adj3 search$) or (electronic adj3 database$) or (computeri?ed adj3 search$) or (internet adj3 search$)).ab. (195210) 41 ((inclusion adj3 studies) or inclusion criteria or selection criteria or predefined criteria or predetermined criteria or (assess$ adj3 (quality or validity)) or (select$ adj3 (study or studies)) or (data adj3 extract$) or extracted data or (data adj2 abstracted)).ab. (236680) 42 ((data adj3 abstraction) or published intervention$ or ((study or studies) adj2 evaluat$) or (intervention$		

	adj2 evaluat$) or confidence interval$ or heterogeneity or pooled or pooling or odds ratio$ or (Jadad or coding) or evidence-based).ab. (975828) 43 34 or 35 or 36 or 37 or 38 or 39 (302486) 44 40 or 41 or 42 (1263196) 45 review.pt. (2135066) 46 44 and 45 (153652) 47 review.ti. (361497) 48 44 and 47 (80800) 49 (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ab,ti. (356094) 50 (retriev$ adj10 (papers or trials or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ab,ti. (17772) 51 43 or 46 or 48 or 49 or 50 (643095) 52 (letter or editorial).pt. (1428373) 53 51 not 52 (634790) 54 exp animal/ (21286346) 55 nonhuman/ (4703468) 56 54 or 55 (22630799) 57 human/ (16725101) 58 56 not 57 (5905698) 59 53 not 58 (606989) 60 ("cochrane database of systematic reviews$" or "the cochrane database of systematic reviews").jn. (12664) 61 59 not 60 (595452) 62 conference abstract.pt. (2168461) 63 61 not 62 (518447) 64 12 and 63 (235)		
Primary Studies			
MEDLINE	1 exp Folic Acid/ (32714) 2 (folic adj2 acid).ab,ti. (15872) 3 folate.ab,ti. (21018)	94	

	4 (vitamin* adj2 B9).ab,ti. (105) 5 (B adj2 vitamin*).ab,ti. (10517) 6 1 or 2 or 3 or 4 or 5 (53842) 7 exp Depression/ (85999) 8 exp Depressive Disorder/ (89303) 9 depress*.ab,ti. (347359) 10 (depress* adj3 disorder*).ab,ti. (37586) 11 (low adj2 mood).ab,ti. (586) 12 7 or 8 or 9 or 10 or 11 (386125) 13 6 and 12 (951) 14 "randomized controlled trial".pt. (408386) 15 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. (894169) 16 (retraction of publication or retracted publication).pt. (8580) 17 14 or 15 or 16 (987927) 18 (animals not humans).sh. (4162343) 19 ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt. (3545568) 20 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt. (56864) 21 17 not (18 or 19 or 20) (732842) 22 13 and 21 (94)		
EMBASE	1 exp folic acid/ (49072) 2 (folic adj2 acid).ab,ti. (20341) 3 folate.ab,ti. (26453) 4 (vitamin adj2 B9).ab,ti. (133) 5 (B adj vitamin*).ab,ti. (2958) 6 1 or 2 or 3 or 4 or 5 (61605) 7 exp depression/ or exp major depression/ (358455) 8 depress*.ab,ti. (461215) 9 (depress* adj3 disorder*).ab,ti. (53468) 10 (low adj2 mood).ab,ti. (901)	166	

	11 7 or 8 or 9 or 10 (590912) 12 6 and 11 (1937) 13 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. (1172480) 14 RETRACTED ARTICLE/ (7965) 15 13 or 14 (1180246) 16 (animal$ not human$).sh,hw. (4001860) 17 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ (4320232) 18 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/ (69778) 19 15 not (16 or 17 or 18) (909799) 20 12 and 19 (166)		
PsycINFO/CINAHL	1 exp Folic Acid/ (496) 2 (folic adj2 acid).ab,ti. (589) 3 folate.ab,ti. (1045) 4 (vitamin adj2 B9).ab,ti. (12) 5 (B adj vitamin*).ab,ti. (191) 6 exp Major Depression/ or exp "Depression (Emotion)"/ (126716) 7 depress*.ab,ti. (238664) 8 (depress* adj3 disorder*).ab,ti. (37492) 9 (low adj2 mood).ab,ti. (636) 10 6 or 7 or 8 or 9 (244777) 11 1 or 2 or 3 or 4 or 5 (1594) 12 10 and 11 (322) 13 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. (173931) 14 (animals not humans).sh. (6315) 15 exp Clinical Trials/ (9436) 16 random*.mp. (152499) 17 15 not 16 (4054) 18 13 not (14 or 17) (173316) 19 12 and 18 (58)	58	

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