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The association of folate and depression: A meta-analysis

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ABSTRACT

Background: Previous research suggested that folate levels play an important role in the etiology and course of depression. However, the literature has been inconsistent with regard to 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.

Methods: Meta-analytic procedures were conducted in accordance with PRISMA guidelines. Studies evaluating folate levels in individuals with and without depression via red blood cell folate, serum folate, or dietary intake of folate methods were identified via PsycINFO and PubMed. Random-effects meta-analysis was conducted using Hedge's *g*, and moderation analysis was used for both folate measurement method and population type. Study heterogeneity was assessed with I^2 and publication bias was qualitatively assessed via funnel plot and quantitatively assessed with the trim-and-fill method and Begg's adjusted rank test.

Results: We found a significant, small effect size, such that individuals with depression had lower folate levels than those without depression, Hedge's $g = -0.24$ (95% CI $= -0.31, -0.16$), $p < 0.001$. Study heterogeneity was high ($I^2 = 84.88\%$), and neither folate measurement method nor population accounted for study heterogeneity.

Conclusions: Individuals with depression have lower serum levels of folate and dietary folate intake than individuals without depression. Given that previous literature suggested folate supplementation improved the efficacy of traditional antidepressant medications, future research on folate supplementation in depression is warranted and clinicians may wish to consider folate supplementation for patients with depression.

Contents

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Depression is a major public health priority that represents the leading cause of global disability (Marcus et al., 2012). Individuals with depression experience serious medical sequelae (Holahan et al., 2010), psychiatric co-morbidity and suicide (Kessler et al., 2003; Minkoff et al., 1973; Takahashi, 2001), and psychosocial impairment (Pratt and Brody, 2008; Rhebergen et al., 2010) because of their disorder. Moreover, depression is a prevalent condition (Hasin et al., 2005; Kessler et al., 2003) that often becomes chronic (Kessler et al., 2012). Despite the considerable burden-of-disease and mortality associated with depression, the best-available evidence-based medications and psychotherapies are not effective for nearly 60% of patients with depression (Eby and Eby, 2010; DeRubeis et al., 2008; Gelenberg et al., 2010). Thus, it appears that core mechanisms of depression are not being targeted in currently available treatments, suggesting that researchers should look to new solutions for depression treatment. One novel area that has shown preliminary promise in the treatment of depression is nutritional adjuvants, with folate receiving much attention.

1. The role of folate in depression

A growing body of research provided evidence that depression may be associated with folate deficiency (e.g., Carney, 1967; Morris et al., 2003; Reynolds et al., 1970). Specifically, research showed that folate deficiency is associated with increased risk for depression (Ramos et al., 2004; Sachdev et al., 2005), more severe depressive symptoms (Reynolds et al., 1970), longer depressive episodes (Levitt and Joffe, 1989), and increased risk of depressive-symptom relapse (Papakostas et al., 2004).

Research on folate metabolism has provided clues for the association of folate deficiency and depression. In the body, folate is ultimately metabolized into S-adenosylmethionine (SAMe) (Alpert and Fava, 1997; Gilbody et al., 2007; Taylor et al., 2004; Tolmunen et al., 2004; Young, 2007). SAMe and folate are important in the production of dopamine, norepinephrine, and serotonin — neurotransmitters implicated in depression — because they affect the rate of production of tetrahydrobiopterin, an antioxidant that is a co-factor in the synthesis of these neurotransmitters (Alpert and Fava, 1997; Coppen and Bolander-Gouaille, 2005; Coppen et al., 1989; Hamon et al., 1986). Thus, if folate is deficient, lower levels of dopamine, norepinephrine, and serotonin result, providing a neurochemical diathesis for depression.

Folate deficiency affects other biological mechanisms of depression. When folate is deficient, homocysteine levels are higher, and research suggested a significant positive association between homocysteine levels and depressive-symptom severity (Bottiglieri et al., 2000a; Tolmunen et al., 2004). Genetic studies implicate the C677T TT (vs. CC) genotype of the methyltetrahydrofolate reductase (MTHFR) enzyme — an enzyme that metabolizes folate — in depression, as meta-analytic evidence suggested that carriers of the TT (vs. CC) genotype are 1.37 times more likely to have been diagnosed with depression (Lewis et al., 2006). Thus, biological research suggested that folate plays an important role in the etiology of depression.

2. The role of folate in the treatment of depressive symptoms

Based on the previously described research, researchers studied the effect of folate level on response to depression treatments. Research suggested that lower folate levels are associated with decreased efficacy of antidepressant medication (Alpert et al., 2003; Coppen and Bolander-Gouaille, 2005; Fava et al., 1997; Lazarou and Kapsou, 2010; Reynolds et al., 1970) and electroconvulsive therapy (Reynolds et al., 1970), even when baseline depression severity and baseline homocysteine and B12 levels are covariates in statistical analyses. Subsequent research found that adjuvant folate supplementation resulted in significantly less severe depression than treatment with antidepressants alone (Taylor et al., 2004), improved general treatment outcomes (Godfrey et al., 1992; Passeri et al., 1993), and shortened inpatient psychiatric hospital stays (Carney and Sheffield, 1970). Other scholars found that treatment of depressive symptoms with folate or SAMe alone resulted in depressive-symptom reduction similar to traditional pharmacotherapies. Specifically, meta-analytic results found that treatment of depression with SAMe alone produced symptom reductions comparable to tricyclic antidepressants (Bressa, 1994). Another study found that treatment of depression with SAMe alone resulted in clinically significant improvement in depressive symptoms for 66% of patients, compared to only 22% of patients treated with imipramine (Bell et al., 1988).

3. The present meta-analysis

The purpose of the present study was to conduct a meta-analysis of the association between folate and depression in individuals with and without depression. A meta-analysis on the association of folate levels and depressive symptoms was previously published (Gilbody et al., 2007). However, since the publication of Gilbody et al. (2007), the number of published empirical studies examining the association of folate and depression has increased with the popularity of nutritional, non-traditional approaches to depression treatment. An updated meta-analysis of the association of folate status and depressive symptoms is warranted because, by increasing the number of studies from the original meta-analysis, a more accurate determination of the effect size of folate deficiency in depression can be determined. Moreover, the

larger number of studies in the current meta-analysis allowed us to conduct moderator and sub-group analyses for population type (e.g., adult, geriatric, perinatal) and folate-measurement method (e.g., red blood cell, intake).

Based on previous literature and meta-analyses, we hypothesized that individuals with depression would have moderately lower folate levels than individuals without depression. Second, we hypothesized that method of folate measurement (e.g., red blood cell, serum, intake) would moderate meta-analytic results, as red blood cell folate assays are regarded as the most accurate measurement of folate, and serum folate assays and nutritional intake have been deemed less accurate (Bottiglieri, 2005; Galloway and Rushworth, 2003). Third, we hypothesized that population type (e.g., geriatric, perinatal, child/adolescent, adult) would moderate meta-analytic results, and specifically hypothesized that folate levels would decrease with age and pregnancy status, based on prior research that folate levels decrease with age (Bottiglieri et al., 1995, 2000b; Selhub et al., 1993) and during pregnancy (Ek and Magnus, 1981; Hall et al., 1976).

4. Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines (Moher et al., 2009).

4.1. Article selection

4.1.1. Literature search

We searched for articles electronically in PsycINFO and PubMed databases through July 2016. In accordance with Gilbody et al. (2007), we used the search terms “folic acid” OR “folate” OR “methyltetrahydrofolate reductase” OR “MTHFR” AND “depressive disorder” OR “depression” OR “depress$” OR “dysthym$” OR “adjustment disorder.” We also conducted hand searches to screen for studies that were not identified through electronic search. Articles yielded from PsycINFO and PubMed searches were pooled and duplicate articles were removed. Study titles were reviewed and articles with titles that indicated assessment of folate in individuals with depression were retained. Abstracts of articles with relevant titles were screened and full-text articles were reviewed. The first and second authors reviewed studies for inclusion.

4.1.2. Inclusion and exclusion criteria

Studies were included based on the following criteria: (1) examined folate levels in individuals with depressive symptoms or depression compared to individuals without depression; (2) assessed folate level using red blood cell folate assays, serum folate assays, or dietary folate intake; (3) written in English or an English translation was available; and (4) reported statistics sufficient to be included in meta-analysis, or authors responded to requests for statistics. We excluded studies that used cerebrospinal fluid taps *only* to measure folate level due to the scarcity of these studies.

4.1.3. Data extraction

To compute Hedge's *g*, sample size, mean, and standard deviation of folate level was extracted for each group. For studies that measured folate using more than one method, we extracted only one measure of folate to prevent a spurious impact of lack of independence on the weighted mean. The most precise folate measure was extracted from each study that reported more than one measure of folate. The literature has deemed red blood cell folate assays as most accurate, followed by serum folate assays, and then dietary folate intake (Bottiglieri, 2005; Galloway and Rushworth, 2003). Thus, if a study reported serum folate assays and dietary folate intake, we extracted serum folate assay data *only*.

4.1.4. Missing data

For those articles that did not report sufficient statistics to be included in meta-analysis, we contacted corresponding authors via email to request the unreported information. We contacted authors up to two times and excluded those studies for which we did not receive necessary data.

4.2. Statistical analysis

Meta-analysis was conducted in R Package Version 3.11 (R Core Team, 2013) using the metafor package (Viechtbauer, 2010). Random-effects meta-analysis was conducted using the DerSimonian-Laird estimator. Rosenthal's fail-safe *N* (Rosenthal, 1979) was used to assess the number of studies needed to produce a non-significant weighted mean effect size.

4.2.1. Effect size heterogeneity

Heterogeneity was assessed using I^2, a statistic that communicates the percentage of between-study variance due to study heterogeneity versus sampling error. I^2 values range from 0.0% (no heterogeneity) to 100% (high heterogeneity); values of 25%, 50%, and 75% have been suggested as benchmarks of low, moderate, and high heterogeneity (Borenstein et al., 2009).

4.2.2. Outliers

Effect sizes greater than three standard deviations from the mean were considered outliers. Results are reported with and without outliers.

4.2.3. Publication bias

We qualitatively assessed publication bias with visual inspection of a funnel plot. Funnel plots graph individual study effect sizes on the x-axis and standard errors of the effect size on the y-axis in relation to the overall effect size. Thus, more precise estimates are located toward the top of the funnel plot, and less precise estimates are closer to the x-axis (Duval and Tweedie, 2000). Degree of asymmetry corresponds to likelihood of publication bias, with increasing asymmetry indicative of increasing likelihood of publication bias. We quantitatively assessed publication bias using Begg's adjusted rank test (Begg and Mazumdar, 1994) and the trim-and-fill method (Duval and Tweedie, 2000), with attention to the right side of the funnel plot.

4.2.4. Methodological moderators

We a priori selected folate measure (red blood cell assays, serum assays, dietary intake) and population (child/adolescent, adult, geriatric, perinatal) as methodological moderators based on previous literature to explain potential study heterogeneity.

5. Results

5.1. Study characteristics

Our final sample included $k = 43$ studies (see Fig. 1) and the characteristics of these studies are presented in Table 1. The total sample size included 8519 individuals with depression and 27,282 individuals without depression.

5.2. Meta-analysis

5.2.1. Overall results

Individuals with (vs. without) depression had significantly

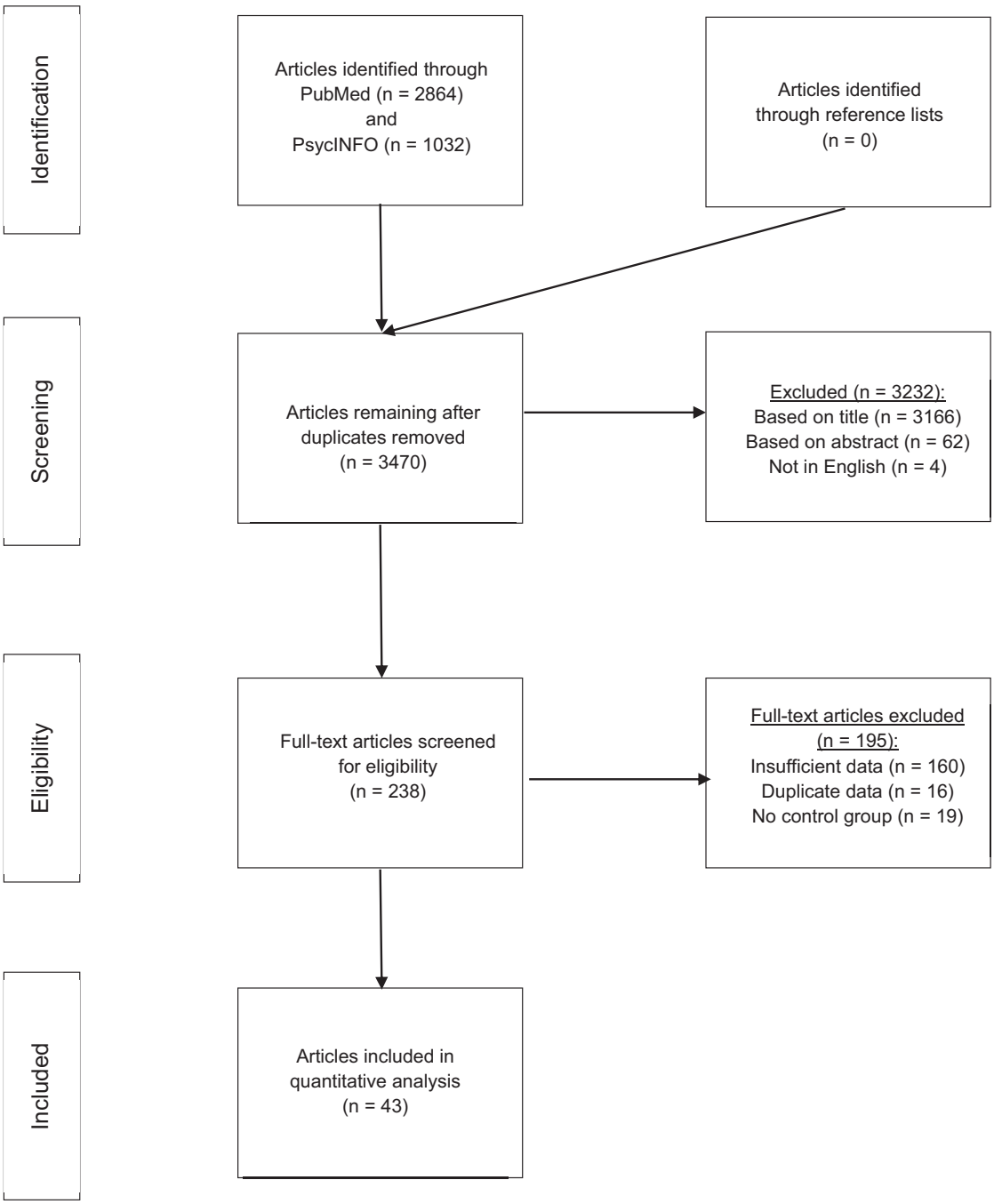

Fig. 1. PRISMA flow chart.

lower folate levels, Hedge's $g = -0.24$, 95% CI $= -0.31, -0.16$, $p < 0.001$, $I^2 = 84.88\%$, and the effect size was small. A forest plot of overall results is presented in Fig. 2, with effect sizes ordered by magnitude within folate measurement method. Results from Rosenthal's fail-safe *N* suggested that 3064 additional studies would be needed to produce a non-significant effect size.

5.2.2. Outliers

Two studies were outliers (Dimopoulos et al., 2007; Wilkinson et al., 1994). Both outliers assessed folate via serum. Exclusion of outliers produced a smaller, but still significant, effect size, Hedge's $g = -0.19$, 95% CI $= -0.25, -0.13$; $p < 0.001$, $I^2 = 77.50\%$.

5.2.3. Publication bias

A funnel plot is presented in Fig. 3. Visual inspection of the funnel plot indicated that publication bias was low because studies were distributed relatively symmetrically around the mean. Quantitative results of publication bias were mixed. Begg's rank correlation test suggested publication bias ($r_\tau = -0.22$, $p = 0.03$). In contrast, the trim-and-fill method supported the visual inspection, suggesting little evidence of publication bias. The trim-and-fill method estimated that one study was missing due to publication bias and inclusion of this missing study with imputation produced an effect size similar to the original model, Hedge's $g = -0.22$, 95% CI $= -0.30, -0.13$, $p < 0.001$, supporting the null hypothesis of no missing studies ($p = 0.25$).

Table 1
Characteristics of included studies.

Author	Year	Location	Sample Size of Depressed Group	Sample Size of Control Group	Age (SD) of Depressed Group	Age (SD) of Control Group	Population Type	Folate Measurement
Abou-Saleh et al.	1998	United Arab Emirates	33	32	38.76 (11.60)	34.78 (11.32)	Adult	Serum
Abou-Saleh et al.	1989	United Kingdom	95	60	59.5 (14.62)	44.7 (23.24)	Adult	Serum
Aishwarya et al.	2013	India	58	45	NR	NR	Perinatal	Serum
Assies et al.	2015	Netherlands	26	73	46.4 (9.5)	44.7 (9.4)	Adult	Serum
Bae et al.	2010	South Korea	50	62	33.84 (3.22)	33.65 (3.66)	Perinatal	Intake
Başoğlu et al.	2009	Turkey	35	32	NR	NR	Adult	Serum
Beydoun et al.	2010a	United States	156	578	47.7 (8.9)	47.9 (9.4)	Adult Men	Serum
Beydoun et al.	2010a	United States	304	643	47.2 (8.9)	48.4 (9.4)	Adult Women	Serum
Beydoun et al.	2010b	United States	117	963	47.4 (2.3)	44.6 (0.8)	Adult Men	Serum
Beydoun et al.	2010b	United States	171	1273	44.9 (1.7)	47.3 (0.9)	Adult Women	Serum
Bottiglieri et al.	1992	United Kingdom	34	10	51.6 (16.8)	51.3 (17.0)	Adult	Red Blood Cell
Bottiglieri et al.	2000a	United Kingdom	46	18	53(16)	34 (10)	Adult	Red Blood Cell
Carney et al.	1990	United Kingdom	152	42	50.9 (16.5)	50.7 (12.1)	Adult	Red Blood Cell
Chong et al.	2014	Singapore	51	658	28.7(6.6)	30.9(5.0)	Perinatal	Serum
Delport et al.	2014	South Africa	86	97	NR	NR	Adult	Serum
Dimopoulos et al.	2007	Greece	33	33	65.8 (6.4)	65.4 (9.1)	Geriatric	Serum
Ebesunun et al.	2012	Nigeria	30	30	37.9 (10.95)	42.5 (5.48)	Adult	Serum
Ford et al.	2013	Australia	236	122	63.1 (0.05)	66.5 (0.8)	Geriatric	Red Blood Cell
Ghadirian et al.	1980	Canada	16	19	50.6 (13.7)	57.4 (21.0)	Adult	Serum
Gougeon et al.	2016	Canada	107	584	75.2 (4)	74.4 (4.3)	Geriatric Women	Intake
Gougeon et al.	2016	Canada	63	614	75.3 (4.1)	74 (4.1)	Geriatric Men	Intake
Kelly et al.	2004	Ireland	93	89	47.7 (NR)	51.2 (NR)	Adult	Serum
Kendrick et al.	2008	United Kingdom	1588	3463	NR	NR	Adult	Red Blood Cell
Kim et al.	2008	Korea	101	631	73.7 (6.3)	72.7 (5.8)	Geriatric	Serum
Kivela et al.	1989	Germany	39	39	75.9 (7.9)	75.5 (7.4)	Geriatric	Red Blood Cell
Lee et al.	1998	China	117	72	41.2 (15.8)	46.5 (12.7)	Adult	Red Blood Cell
Lerner et al.	2006	Israel	36	250	39.4 (13.3)	42.1 (14.2)	Adult	Serum
Lok et al.	2014	Netherlands	137	73	46.4 (9.5)	44.7 (9.4)	Adult	Serum
Lukose et al.	2014	India	119	242	NR	NR	Perinatal	Intake
Miyake et al.	2012	Japan	495	1771	41.7 (9.3)	44.0 (9.8)	Adult	Intake
Murakami et al.	2010	Japan	689	2378	NR	NR	Childhood/Adolescent- Male	Intake
Murakami et al.	2010	Japan	1077	2373	NR	NR	Childhood/Adolescent- Female	Intake
Ng et al.	2009	Singapore	178	491	65.1 (7.5)	65.4 (7.3)	Geriatric	Serum
Pan et al.	2017	United States	33	16	26.21 (7.63)	26.12 (6.11)	Adult	Serum
Park et al.	2010	Korea	65	65	20.6 (0.2)	20.5 (0.2)	Adult	Intake
Payne et al.	2009	United States	111	136	70 (6.3)	71.2 (5.9)	Geriatric	Intake
Penninx et al.	2000	United States	122	478	77.2 (7.9)	77.3 (7.7)	Geriatric Women	Serum
Penninx et al.	2000	United States	100	478	77.4 (8)	77.3 (7.7)	Geriatric Women	Serum
Sachdev et al.	2005	United Kingdom	47	147	62.49 (1.33)	62.47 (1.51)	Geriatric	Serum
Şegul et al.	2014	Turkey	27	68	50.5 (5.3)	52.3 (7.0)	Geriatric	Serum
Seppälä et al.	2012	Finland	429	2377	61 (9)	59 (8)	Adult	Intake
Tiemeier et al.	2006	Netherlands	91	357	73.4 (NR)	72.3 (NR)	Geriatric	Serum
Tolmunen et al.	2003	Finland	228	2215	53.8 ± 4.5	53.0 ± 5.2	Adult	Intake
Tsuchimine et al.	2015	Japan	24	26	16 (2.2)	17.2 (2.4)	Childhood/Adolescent	Serum
Van Dijk et al.	2010	Netherlands	479	2925	29.3 (5.6)	31.4 (4,6)	Perinatal	Serum
Watanabe et al.	2010	Japan	53	33	30.8 (4.7)	30.6 (4.5)	Perinatal	Serum
Wilkinson et al.	1994	United Kingdom	26	21	61.2 (NR)	71.4 (NR)	Geriatric	Serum
Yuan et al.	2008	China	116	80	65.3 (7.9)	64.8 (5.8)	Geriatric	Serum

Note. NR = not reported.

5.2.4. Methodological moderators

Confidence intervals of the subgroup analyses are presented in Figs. 4 and 5 for folate measurement method and population, respectively.

5.2.4.1. Folate measurement method. Folate measurement method did not explain any variance associated with study heterogeneity ($R^2 = 0.00$). Sub-group analyses found that individuals with (vs. without) depression had moderately lower serum folate levels (Hedge's $g = -0.35$, 95% CI = −0.49, −0.20, $p < 0.001$); non-significant differences in red blood cell folate levels (Hedge's $g = -0.10$, 95% CI = −0.31, 0.10, $p = 0.316$); and consumed significantly less folate (Hedge's g = −0.15, 95% CI = −0.22, −0.08, $p < 0.001$).

5.2.4.2. Population. Population type did not explain any of the variance in study heterogeneity ($R^2 = 0.00$). Regarding age, studies with geriatric (Hedge's $g = -0.28$, 95% CI = −0.52, −0.03, $p = 0.027$), child/adolescent (Hedge's $g = -0.14$, 95% CI = −0.25, −0.04, $p = 0.009$), and adult (Hedge's $g = -0.29$, 95% CI = −0.39, −0.19, $p < 0.001$) samples all found a small effect size. Studies with perinatal samples also found a small effect size (Hedge's $g = -0.21$, 95% CI = −0.34, −0.08, $p = 0.001$).

6. Discussion

We tested whether folate levels differed between individuals with and without depression using meta-analysis. Additionally, we tested whether folate level differed by folate measurement method and population with moderator analyses. We included 43 studies with 48 effect sizes in our meta-analysis, compared to Gilbody et al. (2007), which included 11 studies with 11 effect sizes. Results supported previous literature and our hypotheses, and indicated a small effect size, such that individuals with depression had

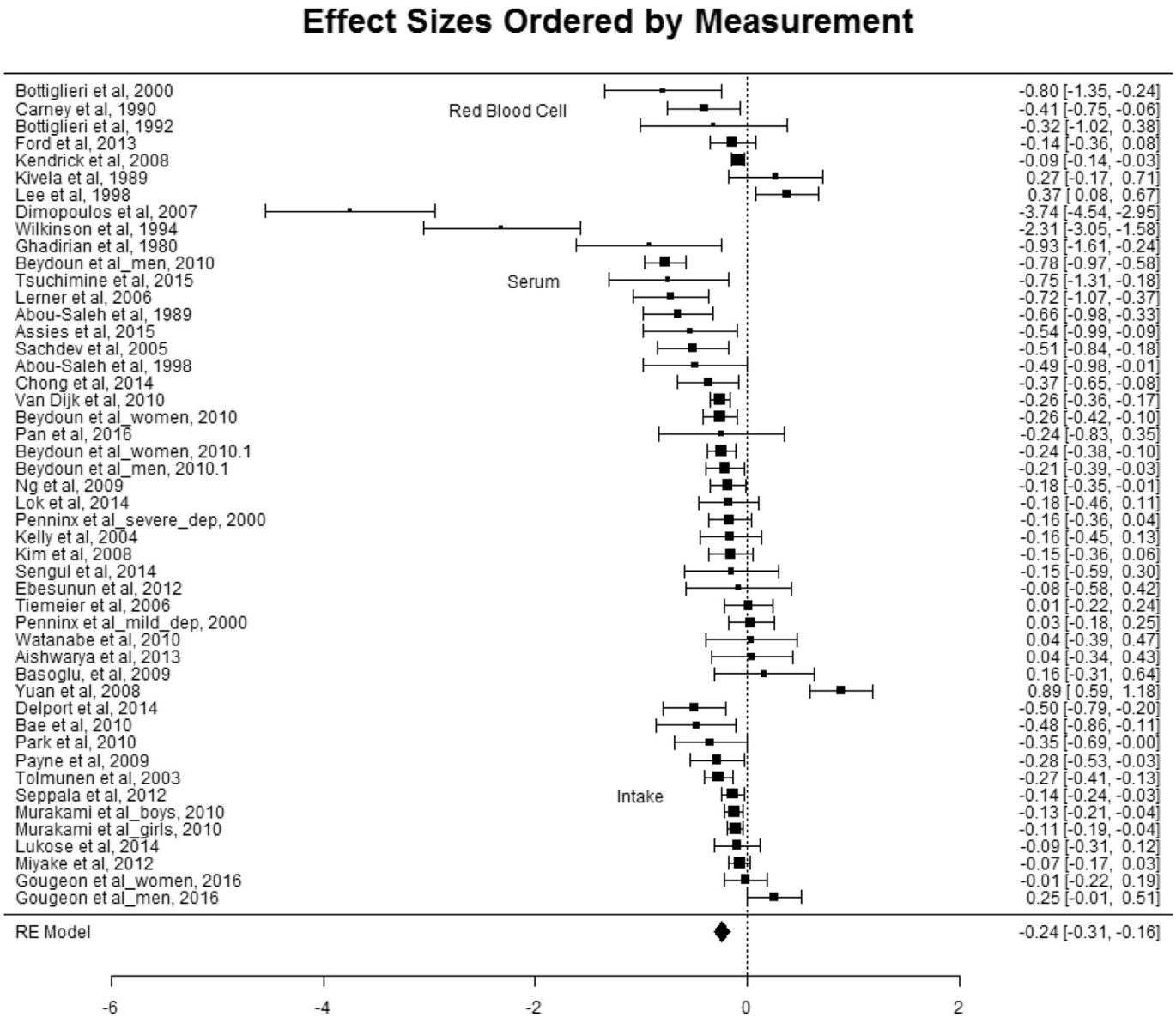

Fig. 2. Forest plot of effect sizes included in meta-analysis.

significantly lower levels of folate than individuals without depression.

Moderator analyses of folate measurement method indicated that individuals with (vs. without) depression consume lower quantities of folate and have lower serum – but not red blood cell – folate levels. It is of particular interest that red blood cell folate measures failed to show a significant association with depression because previous research suggested that red blood cell folate measures are least susceptible to daily fluctuations in diet and are thus the most reliable marker of tissue folate stores (Bottiglieri, 2005; Galloway and Rushworth, 2003). We offer some considerations for this finding. First, the null finding may be due to lack of power, as only seven studies with red blood cell folate as the primary measure met our inclusion criteria. Second, prior work indicated that red blood cell and serum folate measures have a strong, positive association (Galloway and Rushworth, 2003; Jaffe and Schilling, 1991; Magnus, 1975; Phekoo et al., 1997), and that red blood cell and serum folate correlated equally well to liver folate levels (Wu et al., 1975). Thus, serum and red blood cell measures may be equally valid indicators of folate level. Finally, the extra steps required to perform red blood cell assays often result in a less precise measurement than serum folate (NEQAS, 2001); as such, measurement error may have contributed to our null finding. Nevertheless, red blood cell folate stores truly may not differ between individuals with and without depression.

Moderator analysis of population (adult, geriatric, child/adolescent, perinatal) did not explain high study heterogeneity, and all populations showed a small, but significant, effect size of lower folate levels in individuals with (vs. without) depression. However, future reviews of nutritional factors in mood disorders may find it valuable to investigate the role that age and pregnancy status can play in moderating outcomes. For instance, a great deal of literature has examined the interaction of folate with a variety of psychosocial factors in older populations and have related low folate levels to dementia (Cooper et al., 2015; Xu et al., 2015), cognitive impairment (Michelakos et al., 2013), and poorer performance on both recall and recognition memory tasks (Wahlin et al., 1996) and mental status exams (Ramos et al., 2005).

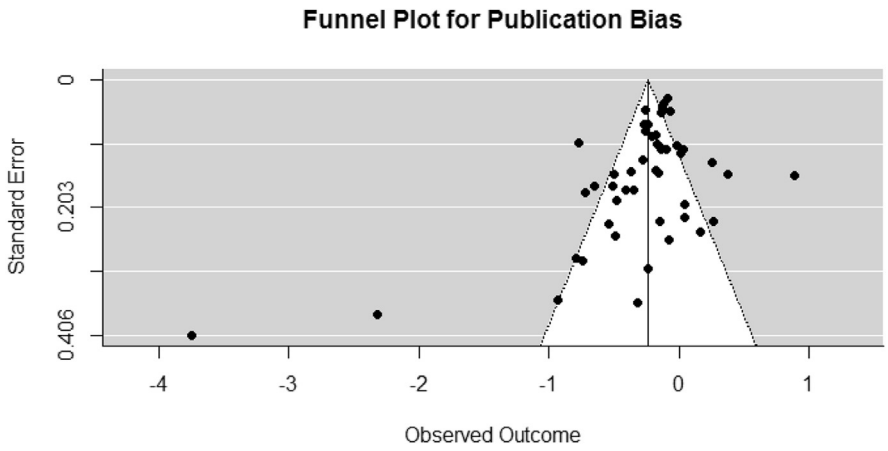

Fig. 3. Funnel plot of effect sizes.

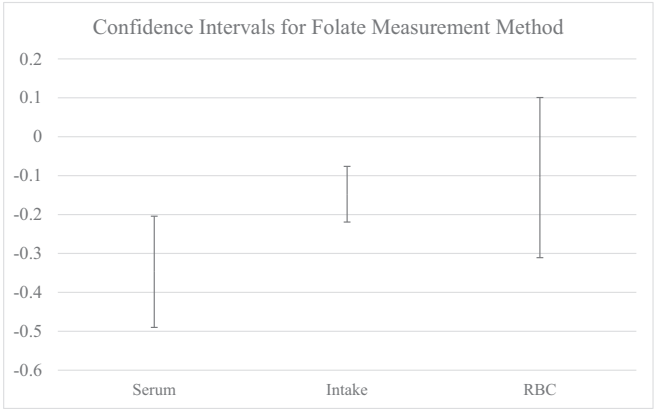

Fig. 4. Line graph of overlapping confidence intervals for folate measurement subgroup analyses. RBC = red blood cell.

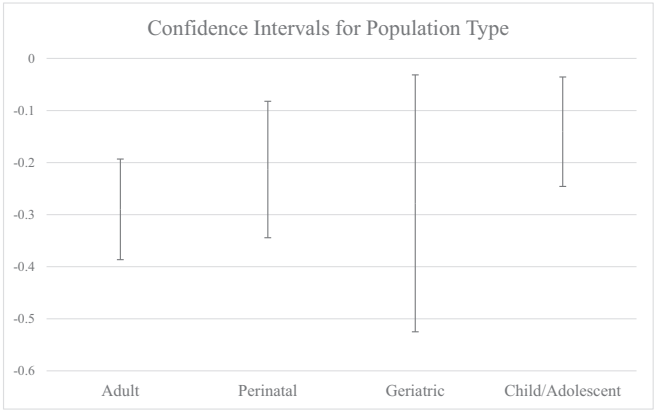

Fig. 5. Line graph of overlapping confidence intervals for population subgroup analyses.

Taken together with previous research that folate supplementation improved the efficacy of depression treatment, results suggest that folate may hold value as adjuvant treatment for individuals with depression. However, this suggestion must be balanced with the fact that findings on the efficacy of folate supplementation in depression have been mixed. Whereas folate supplementation was associated with positive outcomes in individuals with depression, ranging from shorter inpatient treatment stays (Carney and Sheffield, 1970) to improved efficacy of traditional treatments (Alpert et al., 2003; Fava et al., 1997; Reynolds et al., 1970; Taylor et al., 2004), recent meta-analytic results found no significant difference between folic acid supplementation and placebo on depressive symptoms (Sarris et al., 2016). Other research suggested that support for short-term (vs. long-term) supplementation of folate or folic acid is limited (Almeida et al., 2015; Ravindran et al., 2016) and recommended folate supplementation as a third-line treatment (Ravindran et al., 2016). However, long-term folate supplementation may yield more positive outcomes, by reducing onset, severity, and relapse potential of depressive symptoms (Almeida et al., 2015). Another important consideration is that folic acid supplementation may reduce the effectiveness of other psychotropic medications (Geddes et al., 2016). Thus, the interaction of folate and psychotropic medications must be considered before advising such supplementation and future research is needed to better understand the interaction of folate supplementation with psychotropic medications. Despite this, folate appears to be a safe supplement for most individuals (Papakostas et al., 2012). Finally, L-methylfolate is a relatively expensive intervention, yet L-methylfolate may be uniquely helpful for individuals with the C677T TT (vs. CC) genotype of the MTHFR enzyme, implicated in less efficient folate metabolism, because L-methylfolate does not involve the additional breakdown required of synthetic folic acid (Prinz-Langenohl et al., 2009). At a time when many individuals with depression fail to achieve remission via traditional treatment approaches, combined or dynamic treatment approaches may offer promising alternatives and additional research on folate supplementation in depression is thus warranted.

Our study has several limitations. First, results are limited by high study heterogeneity and future research should attempt to better explain the variance of individual study effect sizes by analyzing factors such as continuous age, presence of mandatory folate fortification programs in the countries researched, and other relevant lifestyle factors. Second, the present study assessed associations between depression status and folate levels, and thus results cannot infer causality. Lower folate levels observed in depression may be secondary to poor dietary habits; indeed, our meta-analysis suggested that individuals with depression consume significantly less folate. However, we did not examine the association of the C677T TT (vs. CC) genotype of the MTHFR enzyme with folate deficiency and it is alternatively possible that the less efficient metabolism of folate exacerbates depressive symptoms. Third,

we did not include studies that measured folate with cerebrospinal fluid (CSF) methods. A recent study found that CSF folate levels were deficient, despite adequate serum folate levels, in young individuals with treatment-refractory depression (Pan et al., 2017). Thus, some individuals may have a central (vs. peripheral) folate deficiency and further investigations are needed to evaluate the association of central (or CSF) folate deficiency with depression. Finally, the present study determined folate levels in the presence or absence of depression and future analyses may wish to investigate depression as a continuous (vs. dichotomous) variable to determine if depression severity correlates with folate level.

In sum, the present study found that individuals with depression have significantly lower levels of folate than individuals without depression. The present study extended previous research by including recent investigations and using methodological moderators (e.g., population, folate measurement method). We found that dietary intake of folate and serum levels of folate significantly differentiated individuals with (vs. without) depression, whereas red blood cell levels of folate did not. All populations (geriatric, adult, perinatal, child/adolescent) had significantly lower levels of folate than their non-depressed counterparts. Clinicians may consider folate supplementation for their patients with depression; however, this consideration should be balanced with the fact that further research is warranted to determine if folate is a suitable adjuvant for traditional depression treatments.

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Conflicts of interest

None.

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Author contribution

The first author, AB, conceptualized the idea, wrote the introduction and discussion sections, completed statistical analyses, produced the forest and funnel plots, and created the table of included studies. The second author, KH, edited the manuscript, wrote the methods and results sections, assisted with statistical analyses, and created the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. Both authors reviewed the literature, evaluated studies for inclusion criteria, and emailed authors for data not reported. The third author, NK, provided statistical consultation, assisted with the production of graphical representations of data, and edited the manuscript.

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