

# Is Depression Related to Low Folate Levels in People with Epilepsy? An Observational Study and Meta-analysis

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ABSTRACT

**Background:** Both depression and low serum levels of folate are common in people with epilepsy (PWE), the latter especially in patients on hepatic enzyme-inducing antiepileptic drugs (AEDs). We did a cross-sectional study and a meta-analysis to assess if lower folate levels have any relation with depression in PWE. **Materials and Methods:** Two hundred and one PWE were recruited and assessed for depression using the Inventory of Depressive Symptomatology-Self-Rated (IDS-SR) and Inventory of Depressive Symptomatology-Clinician Rated; serum folate levels were measured in them at the same time. Literature search was carried out and studies with data on depression as well as folate levels in PWE were included. Statistical analysis to determine frequency of depression, low folate levels, and relation between them among our cases and the pooled data from the included studies was done. **Results:** Depression was observed in 65.68% and low serum folate (<4 ng/ml) in 48.75% of PWE (over 80% on older AEDs); there was no statistically significant correlation between them. However, on analyzing the pooled data of six studies including the present, the Fisher's z-transformed correlation coefficient was -0.1690 (95% confidence interval [-0.3175, -0.0124],  $P = 0.0464$ ). **Conclusions:** Depression and low folate levels are common in PWE. Low folate levels have a mild but significant negative correlation with depression in this population, and folate supplementation would be advisable for those on the older AEDs.

**KEYWORDS:** Depression, folate levels, people with epilepsy

## INTRODUCTION

Depression and other psychiatric comorbidities are the strongest predictors of health-related quality of life, irrespective of seizure frequency, seizure severity, employment, or driving status, according to Gilliam *et al.*<sup>[1]</sup> A recent study by Tsegabrhan *et al.* found the prevalence to be 49.3% of the 300 adult people with epilepsy (PWE).<sup>[2]</sup> Causes of depression in these patients are many and may not just depend on the type and frequency of seizures. In India, PWE have far fewer opportunities for education, employment, and marriage, and there is a considerable stigma attached with epilepsy which may also lead to depression.<sup>[3]</sup>

Folate deficiency has been related to depression in many studies, and there is evidence that lower levels

are seen in poor or nonresponders to antidepressant drugs.<sup>[4-7]</sup> In addition, folate supplementation has resulted in better response to these medications.<sup>[6-9]</sup> Several community- and hospital-based studies have shown an association of low folate levels and/or intake through diet with presence of depression.<sup>[10,11]</sup> However, these cover a wide age range and have mostly excluded persons on anticonvulsant medications, particularly those known to cause reduction in folate levels.

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A large proportion of our PWE, as in other developing regions of the world, tend to be young adults. Many are on older antiepileptic drugs (AEDs), as they are available free of cost in government hospitals, and there is poor affordability for the more expensive newer ones. These drugs lower the levels of folate by reducing its absorption or inducing its metabolism. There are meta-analyses that look into the association of older AEDs with low folate levels, and low folate levels with depression, showing association between the variables.<sup>[12,13]</sup> Hence we sought to determine the frequency of depressive symptoms, occurrence of folate deficiency, and a relation between them, if any, among our PWE. Since this relationship of serum folate levels and depression had never been systematically assessed in PWE, we also conducted a meta-analysis.

## MATERIALS AND METHODS

### Subject selection

All patients with diagnosis of epilepsy (focal or generalized), between 18 and 50 years of age presenting to the Department of Neurology, were screened; those on AEDs for at least 6 months, with no seizure recurrence in the last 1 week, and a normal contrast-enhanced computerized tomography scan of the head were recruited. Patients with history of multivitamin intake (or consumption of B-complex group of vitamins) in the previous 3 months, those with cognitive impairment hindering proper administration of rating instruments or those suffering from systemic (renal, hepatic, cardiac, etc.) diseases, active tuberculosis, or other serious illnesses such as malignancy and Acquired Immune Deficiency Syndrome were excluded from the study. In addition, subjects taking two or more alcoholic drinks per day, and pregnant women were excluded. Written informed consent was taken from all recruited individuals; the study was approved by the Institutional Ethics Committee.

### Data collection

Demographic and clinical details of all individuals were recorded. Presence and severity of depression were assessed by the Inventory of Depressive Symptomatology-Self-Rated (IDS-SR) and the IDS clinician-rated (IDS-C) versions in the Hindi language.<sup>[14]</sup> Illiterate PWE had the IDS-SR Hindi version read out to them. Individuals were asked to rate the severity and frequency of specific symptoms present over the last 7 days. Each item was scaled from 0 to 3 with “0” indicating absence of the symptom and “3” standing for the most severe symptomatology during previous 7 days. The scores were added to obtain a total score ranging from 0 to 84. The severity rating was done as: no

depression (score = 0, IDS-SR 0–11; IDS-C 0–13), mild depression (score = 1, IDS-SR 12–23; IDS-C 14–25), moderate depression (score = 2, IDS-SR 24–36; IDS-C 26–38), severe depression (score = 3, IDS-SR 37–46; IDS-C 39–48), and very severe depression (score = 4, IDS-SR 47–84; IDS-C 49–84).

### Serum folate levels

A 5 ml blood sample was drawn from each case at the time of assessment. Serum folate (and Vitamin B12) was done by the enhanced chemiluminescence method (VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System using Intellicheck® Technology) at the Department of Pathology of the hospital. The normal range of serum folate levels at our laboratory is 2.78–20 ng/ml, and that for serum Vitamin B12 level, it is 239–931 pg/ml.

### Methodology for meta-analysis

#### Literature search

An extensive literature search was carried out on multiple databases: PubMed, Web of Science, and Google Scholar, from inception to July 2016 using the following terms: (folate or folic acid) and (depression or depressive disorder or depressive symptoms) and (epilepsy or seizures); cross-references of review articles and studies were also screened. Authors were contacted by E-mail in case the data required for analysis were not provided in the paper. Two reviewers independently conducted the search and scrutiny of studies.

#### Inclusion criteria and exclusion criteria

Cross-sectional, cohort, or case-control studies that recruited PWE as individuals, applied validated screening, and/or severity-rating scales for depression, and performed serum and/or red blood cell (RBC) folate levels were included. Studies that used only dietary analysis for evaluation of folate intake and not serum or RBC folate levels, or did not contain data required for analysis, or if same could not be obtained even after mail to author(s), were excluded from the study.

### Statistical analysis

The Statistical Package for Social Science SPSS version 17 (SPSS Inc. Chicago, USA) version 17 software was used for statistical analysis. Descriptive and analytical statistics including the Pearson’s Chi-square and Spearman correlation tests were used to determine the relationship between depression in PWE and their serum folate levels. The meta-analysis was performed using the statistical package R-3.3.1. Since the objective of the meta-analysis was to determine the degree of association between folate levels and depressive symptomatology, effect sizes were computed in the form of Fisher’s *z*-transformation of “*r*”. This effect size was transformed

from correlation coefficient “r”, “t” statistic, odds ratio (OR) or means and standard deviation, depending on the study in question. In case a study reported results as “not significant,” without accompanying numerical statistic, *z* was assigned a value of 0.00. Data were analyzed using both fixed and random effects model. Sidik and Jonkman method was used for random effects meta-analysis.

## RESULTS

### Demographic and clinical characteristics

Two hundred and one patients were enrolled for the study; their demographic and clinical characteristics are given in Table 1.

### Frequency of depression

Depression was detected in 138 (68.65%) patients if the severity grading was >1 in either of the two scales, i.e., IDS-SR or IDS-C. IDS-SR detected depression in 131 (mild - 65, moderate - 42, severe - 17, and very severe 7), and IDS-C in 112 individuals (mild - 77, moderate - 23, severe - 11, and very severe - 1).

### Frequency of low folate levels

Of 201 PWE, low serum folate levels (<2.78 ng/ml) were observed in 43 (21.39%) patients.

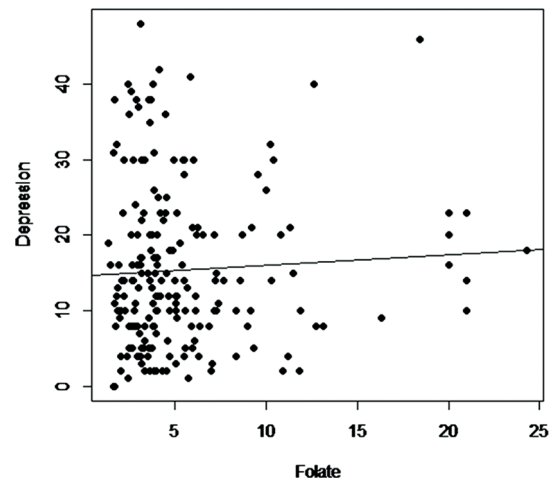
### Depression and low folate levels

Of 131 patients with depression detected on applying IDS-SR, 29 (22.14%) had folate levels lower than 2.78 ng/ml (mild - 16, moderate - 7, severe - 5, and very severe - 1); in 112 individuals with depression detected by IDS-C, there were 27 (23.6%) patients with folate levels lower than 2.78 ng/ml (mild - 19, moderate - 5, and severe - 3).

On the other hand, depression was present in 30 (69.76%) patients among those who had folate

<2.78 ng/ml. However, no significant difference was found in occurrence of low folate levels between patients with or without depression ( $P = 0.993$ ). Figure 1 shows the relation between the serum folate levels and depression among our subjects.

The WHO low cutoff for folate deficiency based on serum homocysteine level is 4 ng/ml.<sup>[15]</sup> Of 98 cases who had folate levels less than this value, 59 had depressive symptoms on the IDS-SR (29 mild, 15 moderate, 12 severe, and 3 very severe) and 54 on IDS-C (33 mild, 12 moderate, 8 severe, and 1 very severe). Among patients with folate levels lower than 4ng/ml, the difference between those with ( $n=68$ ) and without ( $n=30$ ) depression on either scale was also not statistically significant ( $P = 0.827$ ). The OR for depression with folate levels <4 ng/ml was 0.91 (95% confidence interval [CI] [0.52–1.58],  $P = 0.74$ ). The clinician-rated IDS-C was used to calculate the OR.



**Figure 1:** Scatter diagram of relation between serum folate levels (ng/ml) and depression (scores of Inventory of Depressive Symptomatology) among our patients

**Table 1: Demographic and clinical characteristics of cases (n=201)**

Variable	Depressive symptoms present Score $\geq 1$ in IDS-SR and/or IDS-C (n=138)	Depressive symptoms absent Score=0 in IDS-SR and/or IDS-C (n=63)	P-values
Gender (female/male)	65/73	20/43	0.0587*
Mean age (years) $\pm$ SD	26.95 $\pm$ 8.401	27.41 $\pm$ 8.39	0.723**
Literate (able to read at least one language) (n=174)	126	48	0.0996*
Employed, % (n=112)	64	48	0.7182*
Single (n=89) (unmarried/widowed/separated)	66	23	0.1785*
Mean duration of epilepsy (years) $\pm$ SD	7.94 $\pm$ 6.25	7.04 $\pm$ 7.21	0.89**
Mean monthly frequency of seizures in the last 1 year $\pm$ SD	4.51 $\pm$ 10.45	2.71 $\pm$ 4.423	0.422**
Focal seizures	104	48	0.8991*
On monotherapy	58	26	0.9194*
On older AED(s)	108	56	0.1080*

\*P-value of Chi-square test, \*\*Student's *t*-test. SD: Standard deviation, AED: Antiepileptic drug, IDS-SR: Inventory of Depressive Symptomatology-Self-Rated, IDS-C: Inventory of Depressive Symptomatology-Clinician Rated

### Correlation analysis

Serum folate levels showed a positive correlation of 0.0233, an anomalous result indicating that the folate status has no impact on depression scores (IDS-C were used),  $P = 0.438$  [Figure 1]. Duration of epilepsy before recruitment was inversely related to the serum folate levels ( $\rho = -0.27$ ,  $P = 0.265$ ) and it had a weak positive relation with depression scores ( $\rho = 0.086$ ,  $P = 0.241$ ). The Spearman correlation between serum levels of folate and Vitamin B12 was 0.139, which was statistically significant ( $P = 0.048$ ).

### Results of the meta-analysis

There were 51 studies in the search results of PubMed, 19 in Web of Science, and 1820 in Google Scholar, using keywords (Section 2.5), and 10 studies from cross-references of original and review articles. Eleven studies, all hospital-based and observational, were shortlisted and read in detail. Five studies were included [Table 2]; authors of 2 others were sent mails to, as the necessary data were neither available in the paper nor was there any supplementary information. The pooled analysis was done using data from these four and the present study.<sup>[16-20]</sup>

**Table 2: Brief description of studies included in meta-analysis**

Study/year/reference	Study design	Cases	Controls	Scale used for measuring low folate depression	Method of folate estimation/definition of	Effect size	Quality score
Trimble, 1980 <sup>[20]</sup>	Cross-sectional	$n=312$ children with epilepsy, folate in 294	$n=96$ , general medical outpatients without epilepsy or known disorders of folate metabolism	Clinical four-point rating scale	Radioimmunoassay serum folate $<3 \mu\text{g/L}$ ; mean RBC folate in controls: $99.19 \mu\text{g/L} \pm 49.58$	Significant difference between serum and RBC folate in depressed and nondepressed by $t$ -test, $P < 0.001$	9/15, fair
Edeh and Toone, 1985 <sup>[19]</sup>	Cross-sectional	$n=82$ persons with active epilepsy	None	CIS	Microbiologic assay/ serum folate $<3 \mu\text{g/L}$ ; RBC folate $<150 \mu\text{g/L}$	$t=3.41$ , $P < 0.001$ , for difference of serum folate between the group with depressive neurosis and patients without psychiatric morbidity	6/15, poor
Rösche <i>et al.</i> , 2003 <sup>[18]</sup>	Cross-sectional	$n=54$ intractable epilepsy inpatients	None	SDS	Ion-capture assay/ $<3.5 \text{ ng/mL}$ (immunoassay)	( $r=0.311$ , $t=2.36$ , $P=0.022$ ) $t$ -test, two-tailed, $t=1.596$ , degrees of freedom 33,19, $P=0.12$	8/15, fair
Rosche <i>et al.</i> , 2003 <sup>[17]</sup>	Cross-sectional	$n=46$ , chronic epilepsy inpatients	None	SDS	Ion-capture assay/ $<3.5 \text{ ng/mL}$ (immunoassay)	$P < 0.05$ between cases with and without depressive symptoms. Correlation coefficient: $r=-0.37$ ( $t=-2.64$ ; $P < 0.02$ )	8/15, fair
Bochynska <i>et al.</i> , 2012 <sup>[16]</sup>	Longitudinal	51 adults with chronic epilepsy, 30 adults with newly diagnosed epilepsy	No healthy controls	BDI	Immunoassay	No significant correlation between serum folate and depression scores (numerical values not given)	9/15, fair

CIS: Clinical Interview Schedule, SDS: Self-Rating Depression Scale, BDI: Beck Depression Index, RBC: Red blood cell

### Effect size

This meta-analysis included data from 758 participants. A fixed effects model of the pooled data detected substantial heterogeneity (73.56%) and therefore random effects model was used for further analysis. Pooling of all estimates showed a mild, negative but significant relationship between folate status and depression, Fisher's  $z$ -transformed correlation coefficient was  $-0.1691$  (95% CI  $[-0.3356, -0.0027]$ ;  $P = 0.0464$ ) with a high degree of between-study statistical heterogeneity ( $I^2 = 77.94\%$ ) [Figure 2]. The 95% prediction interval for this model was  $[-0.55, 0.21]$ .

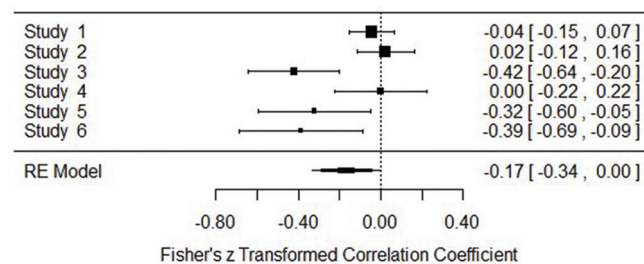
### Meta-regression and subgroup analysis

Given the small number of studies and missing data, no independent moderating variables could be found.

RBC folate was performed in two studies only – Edeh *et al.* and Trimble *et al.*; both showed a significant correlation of RBC folate with serum folate levels. Trimble *et al.* found significantly lower RBC folate levels in cases with depression, compared to those without. Among other variables, correlations with seizure type, frequency, or duration were not given in most studies; Edeh and Toone found no correlation with age, duration of epilepsy, or seizure frequency. In addition, serum Vitamin B12 levels were not correlated with either serum or RBC folate concentrations in this study. Intelligence quotient (IQ) was done in one (Trimble *et al.*) but was not analyzed for association with depression; the studies by Rösche *et al.* and the present study recruited cases with IQ more than 70.<sup>[16-19]</sup>

### Sensitivity analysis

Data from three studies when removed from the analysis (leave-one-out analysis) kept the Fisher's transformed correlation coefficient significant and negative - those of Trimble *et al.* ( $n = 294$ ), Bochynska ( $n = 51$ ) and the present study ( $n = 201$ ). The study whose removal reduced the heterogeneity the most was Edeh *et al.* Heterogeneity was brought down, however to 68%, which is not a large difference, and the pooled Fisher's



**Figure 2:** Meta-analysis of Fisher's  $z$ -transformation of " $r$ " between folate levels and depression in people with epilepsy. Overall variation attributed to between-study heterogeneity,  $I^2 = 77.94\%$  (Studies 1–6 in following order: MR Trimble, 1980; Ramanujam B (unpublished); J Edeh, 1985; A Bochynska, 2012; J Rosche, 2003 I; J Rosche, 2003 II)

transformed correlation coefficient no longer remained statistically significant.

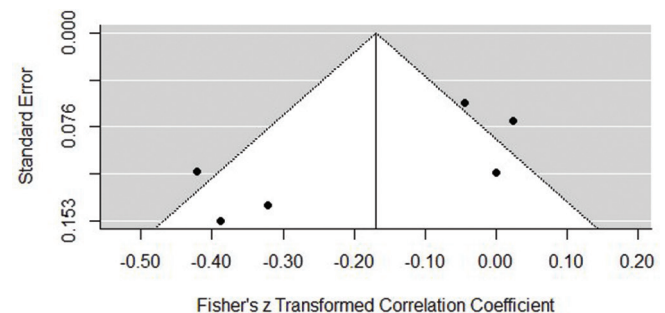
### Publication bias

Visual inspection of the funnel plot [Figure 3] suggests only a mild publication bias, as very few negative studies are published. The Egger's regression for forest plot asymmetry was not statistically significant ( $P = 0.0516$ ).

## DISCUSSION

PWE are known to have psychiatric comorbidities, particularly depression. In this study, both low folate levels and depression are present in more than half of the cases. Depression itself leads to poor intake and if long-lasting, nutritional deficiencies. However, we did not find any significant difference between serum folate levels in depressed and nondepressed patients we recruited. Although we do not have epidemiological data to support this, the reason no association was found may be attributed to the fact that a sizeable number of our healthy population could have folate in the low-normal range. In addition, most of our cases were on older, enzyme-inducing AEDs, came from low socioeconomic backgrounds, and may have similar (wrong) cooking practices that lead to the loss of these vitamins. Therefore, low-normal serum folate levels were noted in many of our patients, and had significant correlation with Vitamin B12 levels.

Depression was found in about 68% of our sample; the studies by Rosche *et al.* also reported a similar value of 63% in their cases.<sup>[16,17]</sup> Depression seems to be higher in our PWE, despite the fact that in the studies by Rosche individuals were inpatients, probably with more severe epilepsy. The study by Edeh and Toone recruited PWE from general practices and depression was seen in only 19 of the 82 recruited cases.<sup>[19]</sup> The different rates of depression can be explained by cultural differences between our population and theirs. Here, patients feel stigmatized and have few opportunities for education and occupation. There is more dependence on family members and PWE are discriminated against when it comes to marital alliances.<sup>[21,22]</sup> Even expressed emotions



**Figure 3:** Funnel plot of various studies in the meta-analysis

from key caregivers are seen to be associated with depression in these patients.<sup>[23]</sup> It is also possible that cases with milder depression have been detected with the rating scales used, resulting in the higher numbers. IDS-C and IDS-SR include not only the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criterion symptoms, but also the other commonly associated features such as anxiety, irritability, and items relevant to melancholic, or atypical symptoms.<sup>[14]</sup> Since the IDS is a screening instrument only, we referred all those with scores indicating depressive symptomatology to the Psychiatry Department for appropriate management.

Our meta-analysis results show that folate levels have a small but significant association with depressive symptoms in PWE, which corresponded to an  $R^2$  value of just 2.8%. That is, <3% of the variation in depressive symptoms of PWE can be accounted for by their folate status. The prediction interval for this model ranges from -0.55 to 0.21. Even though we can expect a negative association between folate and depression, this may not hold true for all populations, as the interval contains the value 0 and there is substantial heterogeneity in this model. High between-study heterogeneity in our meta-analysis could have been due to the different methods of folate estimation, normal values and differences in the age-ranges, the study by Trimble having recruited children below 16 years of age.<sup>[19]</sup> The study designs were similar, all being cross-sectional observational studies, except one Bochynska *et al.*, who conducted a longitudinal study. Only one study by Froscher *et al.* recruited healthy controls, but since the relevant summary statistics for their data were not available, their study was not used for analysis. Publication bias was not significant despite a relative lack of studies with negative results. We were limited by the small number of studies done in this population.

The meta-analysis by Gilbody *et al.* also computed a small effect size of 1.55, despite a much larger sample of over fifteen thousand participants. They included 11 community- and hospital-based studies but none with PWE.<sup>[13]</sup>

The meta-analysis of ten studies by Gorjipour *et al.* suggests that patients on carbamazepine but not those on valproate have lower serum folate levels.<sup>[12]</sup> There was over-representation of patients on phenytoin among those with low levels of folate, in the Trimble study.<sup>[19]</sup> Bochynska *et al.* found that serum folate was lower in the patients treated with both Valproate and Carbamazepine; newly diagnosed PWE treated with the former drug also developed lower levels. They also

observed that though there was no correlation of serum folate levels (or serum homocysteine, Vitamin B12 levels) with depression measured by Beck Depression Index at baseline, there was a significant improvement in the scores after supplementation with the vitamins for 1 year.<sup>[20]</sup> Valproic acid affects folate-metabolism by inhibiting the glutamate formyltransferase and changing the balance between various folate forms.<sup>[24]</sup>

A single measurement of serum folate cannot differentiate between a transitory reduction in dietary folate intake and chronic deficiency states. RBC-folate concentrations are useful in determining long-term folate status because RBCs accumulate folate only during erythropoiesis, and have a 120-day lifespan.<sup>[25]</sup> Since RBC folate levels were done in two studies only (Edeh *et al.* and Trimble *et al.*), a meta-regression was not possible. Both studies showed a significant correlation between RBC and serum folate levels.<sup>[18,19]</sup>

A note about the rating scales: In the data we have presented, the number of patients detected to be depressed was more by the self-rated IDS-SR than by clinician-rated IDS-C. This trend was observed among the studies we included for analysis as well, the two that used self-rated scales (studies by Rosche *et al.* and Bochynska *et al.*) got depression rates over 60%, but the ones that used clinician-rated scales (Trimble *et al.* and Edeh *et al.*) found only 5%–30% of their PWE depressed. Although overrating of their symptoms by patients themselves may be the implication, the studies that used clinician-rated scales were both done in the early 1980s, so may not have included some of the more recently recognized symptoms.

The monoamine hypothesis associates deficiency of serotonin or noradrenaline with depression.<sup>[26]</sup> Folic acid, through the folate-cycle, provides methyl groups to *s*-adenosylmethionine for the synthesis of these monoamines.<sup>[27]</sup> This is the cause of raised serum homocysteine levels in folate deficiency. Tetrahydrobiopterin is a cofactor in the hydroxylation of phenylalanine, tyrosine, and tryptophan (rate-limiting step in the synthesis of the monoamine neurotransmitters) and folate is required to form the initial compound, guanosine triphosphate, of the biopterin synthesis.<sup>[28]</sup> The community-based study by Tiemeier *et al.* suggests that the relation between folate and pterins is altered in the depressed elderly, though they found no association between the concentration of biopterin or neopterin with depressive symptoms or depressive disorders.<sup>[29]</sup>

Although folic acid is involved in one-carbon metabolism in the entire body, the levels of free folate in the form of methylfolate are about 4 times higher in the cerebrospinal fluid than in the plasma, both

levels appearing to be directly related.<sup>[30-32]</sup> Levels of methylfolate in the cerebrospinal fluid are also strictly regulated by an active transport mechanism by the blood–brain barrier, possibly due to the excitatory/proconvulsant properties of folate.<sup>[33]</sup>

As with folate, higher serum homocysteine levels have been correlated with depression. Hyperhomocysteinemia is also a known risk factor for vascular diseases such as stroke.<sup>[34-36]</sup> In a study by Sachdev *et al.*, white-matter hyperintensities had significant correlations with both homocysteine and depressive symptoms.<sup>[37]</sup> Two autopsy studies by Thomas *et al.* showed that the white matter intensities seen in the magnetic resonance imaging of patients with depression were ischemic lesions.<sup>[38,39]</sup>

## CONCLUSIONS

Low serum folate levels have a significant correlation albeit small association with depression in PWE. It is also associated with neural tube defects in fetuses exposed to lower maternal folate levels.<sup>[40]</sup> Therefore, given the high prevalence of epilepsy in developing countries and poor availability of foods fortified with vitamins, it may be prudent to supplement folate in our PWE on the enzyme-inducing AEDs.

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## Conflicts of interest

There are no conflicts of interest.

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