



## Review article

## Lower folate levels in schizophrenia: A meta-analysis



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## ABSTRACT

This meta-analysis aimed to estimate the association between folate level and schizophrenia in order to provide the evidence for the treatment of schizophrenia. Data were extracted from all the studies meeting our inclusion and exclusion criteria. The association between the folate level and schizophrenia was evaluated by the standardized mean difference (SMD) and 95% confidence interval (CI). The 20 published articles of our meta-analysis included 1463 (53.4%) cases and 1276 (46.6%) controls. The folate level was significantly lower in schizophrenia cases than in healthy controls. Subgroup analysis showed the folate level was lower in cases from Asia subgroup than in healthy controls. Sensitivity analysis showed that the current results were credible and reliable and the funnel plots indicated no publication bias in our meta-analysis. Our study indicates that schizophrenia patients may have lower folate levels. More epidemiological and laboratory studies are still needed to confirm whether it is necessary to supplement folate in schizophrenia patients.

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## 1. Introduction

The psychopathological manifestations of schizophrenia consist of separation from reality with delusion formation, disorganized behavior, hallucinations, and emotional dysregulation (Millier et al., 2014).

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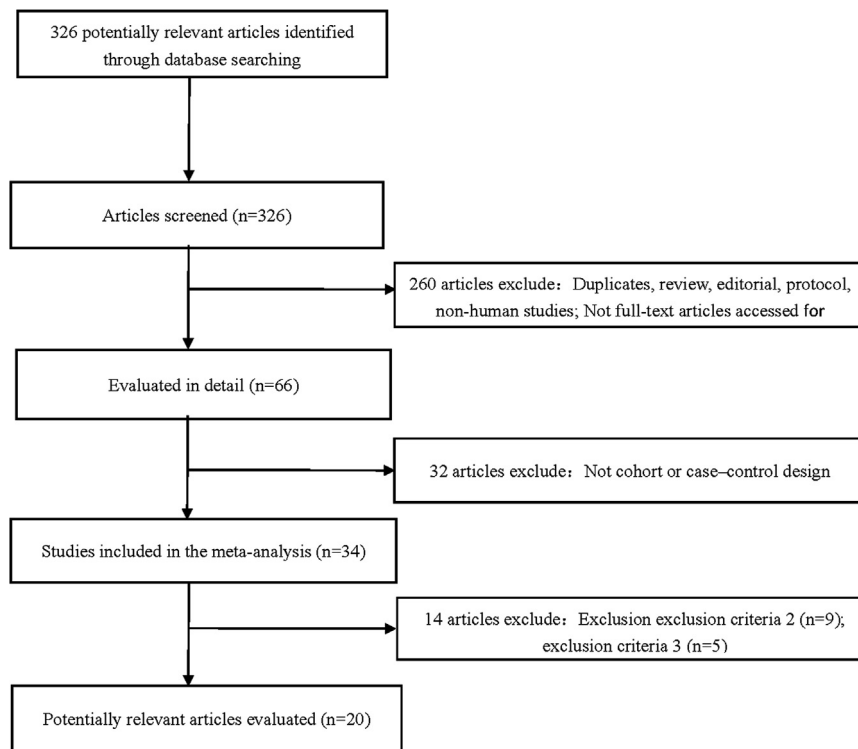


Fig. 1. Flow chart depicting exclusion/inclusion of individual studies for meta-analysis.

It is a debilitating disorder that affects 1% of the population worldwide (Arroll et al., 2014). Schizophrenia evolves in cycles of remissions and relapses (Millier et al., 2014) with financial burden and humanistic burden on society (Abouzaid et al., 2010).

Folate is one of the B vitamins which is required for cell division and cell maintenance and folate is the re-methylation of plasma homocysteine to methionine (Mitchell et al., 2014). Studies have been reported that folate is essential for neuronal function (Czeizel et al., 2013). Severe folate deficiencies may be linked to the increased risk of neurodevelopmental disorders, psychiatric diseases and dementia (Mitchell et al., 2014). The association between folate level and schizophrenia is still controversial (Ayesa-Arriola et al., 2012; Bouaziz et al., 2010; Chen, 2014; Eren et al., 2010; Feng et al., 2009; Garcia-Miss Mdel et al., 2010; Haidemenos et al., 2007; Hei et al., 2014; Kim and Moon, 2011; Mabrouk et al., 2011; Misiak et al., 2014; Muntjewerff et al., 2003; Ozcan et al., 2008; Petronijevic et al., 2008; Qian et al., 2009; Saedisomeolia et al., 2011; Song et al., 2014; Zhang et al., 2010; Zhang et al., 2007; Zhu et al., 2010). Several studies revealed a positive relationship between folate deficiency and schizophrenia (Chen, 2014; Kim and Moon, 2011; Mabrouk et al., 2011). While other studies did not find that folate deficiency increased the risk of schizophrenia (Ayesa-Arriola et al., 2012; Bouaziz et al., 2010; Garcia-Miss Mdel et al., 2010; Ozcan et al., 2008). Therefore, the relationship needs to be further evaluated.

Taking all findings into consideration, we performed this meta-analysis to evaluate the association of them and then to provide the evidence for the treatment of schizophrenia.

## 2. Methods

### 2.1. Literature searches

We performed a systematic literature search to identify eligible relevant studies that reported the folate status of schizophrenia

and were published in English or Chinese in an electronic database. Search terms included “schizophrenia OR psychotic disorders OR psychosis”, “folate OR folic acid OR vitamin 9”. PubMed, EMBASE literature database were used to search the studies published in English. And China Biology Medical (CBM), China National Knowledge Infrastructure (CNKI), VIP information (VIP) were used to search the studies in Chinese. Searches were limited to articles about human studies before the end of April 2015.

### 2.2. Inclusion and exclusion criteria

Inclusion criteria of the studies were met if they (1) used a cohort or case-control design; (2) assessed a group of unaffected controls (control subjects were selected from healthy volunteers who were recruited from students, company employees and so on documented to be free from psychiatric problems and histories of mental illness); (3) diagnosed schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria by at least 2 psychiatrists on the basis of extensive clinical interviews and a review of medical records; (4) had available folate levels of participants .

Exclusion criteria of the studies were met if they (1) did not focus on evaluating the folate levels on schizophrenia; (2) did not report the exact values of folate level; (3) included unhealthy control groups; (4) were repetitive publications from the same datasets by the same or different authors.

### 2.3. Data extraction

Data were extracted from all the studies that met our inclusion and exclusion criteria. We designed a data form in Excel to extract the relevant data for our review. Two investigators abstracted information independently for each eligible article, and reached a consensus on all the items through discussion of disagreements. Detailed information about the index test was extracted from the studies which included first author, publication year, country,

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