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Serum folate levels in schizophrenia: A meta-analysis

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ABSTRACT

To clarify the relationship between serum folate and schizophrenia (SZ) risk, the meta-analysis was conducted. PubMed, Embase, and Web of Science were searched without language restrictions. Weighted mean difference (WMD) as a summary statistic was used in this meta-analysis. Subgroup analyses by publication language (English and non-English), ethnicity (Caucasian, Asian, African, Latino, and mixed population), duration (acute, chronic, patients including both acute and chronic SZ, and not mentioned about either chronic or acute), measurement time (before drugs using and after drugs using), gender (male and female) and age (<50 years old and >50 years old) were performed. Power analysis was also conducted to detect the reliability of the meta-analyses' results. In summary, the subgroups which failed to detect significant decreased associations were always with lower statistic power and could not be confirmed. The results supported that decreased serum folate was associated with SZ risk in total studies and subgroups of English publications, Caucasians, Asians, acute SZ patients, measurement after drugs using in SZ patients, and age <50 with the great enough powers, respectively. In conclusion, the present meta-analysis found that folate deficiency is associated to SZ, and subgroups which did not reach enough statistical power need further investigation in the future.

1. Introduction

Schizophrenia (SZ) is one of the most mysterious mental disorders (van Os and Kapur, 2009), and it affects about 1% of the population (Howes and Murray, 2014). Although pathophysiology of SZ has not been fully understood, biological studies support that one-carbon (C1) metabolism including high homocysteine (Hcy) levels might play an important role (Krebs et al., 2009). High Hcy in serum, namely hyperhomocysteinemia (HHcy), through oxidative stress by Hcy, may lead to neurodegeneration, which is one of the characters of SZ (Kalani et al., 2014; Pino et al., 2014). By folate-dependent reactions, most Hcy is converted to methionine (Rogers et al., 2007), which can reduce Hcy levels. In an animal experiment (Kalani et al., 2014), HHcy mice's brain showed high-nitrite levels (known to cause neuronal damage with reactive oxygen species (ROS)), high-malondialdehyde (a measurement of free radical generation and an end product of lipid peroxidation), and low glutathione (antioxidants) levels, which suggested brain damage and neurodegeneration. HHcy mice with folate supplementations could reduce those oxidative stress products and increase glutathione levels. On the other hand, folate is important to generate S-adenosylmethionine (SAM) for DNA methylation, which plays an important role in controlling of gene and, eventually, protein expression (Kalani et al., 2014). If folate deficiency or HHcy occurs, DNA methylation will be altered by changing DNA methyltransferase (DNMT) activity. These changes may impact the Hcy-mediated vasculopathies including loss of extracellular matrix collagen, endothelial dysfunction, and disruption of the blood–brain barrier (Kalani et al., 2014). Vasculopathies will give rise to neurodegeneration, and ultimately, SZ. Thus, folate could be a protective factor of SZ. Dietary folate intake is assessed by multiple instruments such as food frequency questionnaire (FFQ), and 24-hour dietary recall (24HDR) so on and so forth, which will induce self-reported measurement errors (Park et al., 2013). Biomarkers (serum folate and red blood cell (RBC) folate) may reflect the bioavailability of the actual nutrient, and have been increasingly used as a surrogate for actual dietary intake (Park et al., 2013). The RBC folate concentration is determined by the erythropoiesis process itself, which is dependent on erythropoietin production and the availability of iron, vitamin B12 and zinc (Park et al., 2013).

Abbreviations: SZ, schizophrenia; C1, one-carbon; Hcy, homocysteine; ROS, reactive oxygen species; SAM, S-adenosylmethionine; DNMT, DNA methyltransferase; FFQ, food frequency questionnaire; 24HDR, 24-hour dietary recall; RBC, red blood cell; SD, standard deviation; WMD, weighted mean difference; CI, confidence interval; NM, not mentioned; SAH, S-adenosylhomocysteine; THF, tetrahydrofolate

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RBC folate is affected by the erythrocyte life span (about 120 days), while serum folate as an indicator is associated with folate intake in recent time (Park et al., 2013). Thus, serum folate is considered as an appropriate marker for folate status in epidemiological studies (van Wijngaarden et al., 2013). In addition, folate is mainly measured in serum and the cellular levels are seldom (Krebs et al., 2009). Thus, we selected serum folate as an index rather than diet folate or RBC folate concentration to measure the relationship between folate and SZ risk.

In 1967, Carney first investigated the relationship between serum folate and SZ among Caucasians in England, and got none significant result (Carney, 1967). After that, several researchers also confirmed the same relationship in different ethnicities and countries (Gundersen, 1969; Hermesh et al., 1988; Susser et al., 1998). In 1999, Herran et al. (1999) found a negative significant relationship among Caucasians in Spain. In the following years till present, no consensus is reached on serum folate associated with SZ risk according to the original studies (Goff et al., 2004; Lee et al., 2006; Lerner et al., 2006; Haidemenos et al., 2007; Zhang et al., 2007; Ozcan et al., 2008; Petronijevic et al., 2008; Ozsoy et al., 2009; Qian et al., 2009; Trujillo et al., 2009; Bouaziz et al., 2010; Eren et al., 2010; Garcia-Miss Mdel et al., 2010; Zhu et al., 2010; Kim and Moon, 2011; Mabrouk et al., 2011; Saedisomeolia et al., 2011; Ayesa-Arriola et al., 2012; Chen et al., 2014; Misiak et al., 2014; Song et al., 2014). Meta-analysis can pool all the conflicting results, enlarge sample size and get a reliable conclusion. However, till now, no meta-analysis was found about this relationship. In addition, publication language (English and non-English), ethnicity (Caucasian, Asian, African, Latino, and mixed population), duration (acute, chronic, patients including both acute and chronic SZ, and not mentioned about either chronic or acute), measurement time (before drugs using and after drugs using), gender (male and female) and age (<50 years old and >50 years old) might also affect the results. To explore this topic systematically, we performed the meta-analysis and the relevant subgroup analyses.

2. Methods

2.1. Literature search

Three international electronic databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) (1950～), Embase (http://www.embase.com/) (1947～), and Web of science (http://www.webofknowledge.com/) (1900～) were searched. We used the following search strategy: ("schizophrenia" or "schizophrenic") and ("folate" or "folic acid" or "folvite") and ("serum" or "plasma" or "blood" or "circulation"). We also checked the references in the included publications and related reviews for supplement. We performed the last search on February 22, 2015 without the language restrictions.

2.2. Inclusion and exclusion criteria

Publications were included if they: (1) concerned serum folate levels; (2) compared between SZ patients and healthy controls; (3) study designs were case-control, cross-sectional, nested case-control or cohort study. The exclusion criteria: (1) if the publications had duplicated or overlapping cases, we selected the largest sample size or the recent publications, and excluded the others; (2) only reported SZ cases without healthy controls; (3) insufficient data; (4) reviews.

2.3. Data extraction

We extracted the following data in each identified publications: first author, publication year, publication language, country, region, ethnicity, number of SZ cases and healthy controls, mean and standard deviation (SD) of the concentrations of serum folate in each SZ cases and healthy controls, classification of SZ duration, measurement time, gender, and age. The unit of serum folate is μg/L; to convert nmol/L to μg/L, data divide by 2.266 (Carney, 1995). To ensure the correction of the data, two investigators extracted the data independently, and inconsistency was solved by the judgment of the third investigator.

2.4. Statistical analysis

Software programs Review manager (version 5.3) and Stata (version 12.0) were used to perform the statistical analysis. We used weighted mean difference (WMD) as a summary statistic in this meta-analysis, because effect measures for continuous outcomes (concentration of the serum folate) in all studies are made on the same scale (Higgins and Green, 2011). Heterogeneity was measured by Q statistic and I^2 statistic. When $P<0.10$ or $I^2>50\%$, there was heterogeneity in the meta-analysis, and random-effects model was used; otherwise, fixed-effects model was used (Higgins and Green, 2011). Subgroup analyses by publication language (English and non-English), ethnicity (Caucasian, Asian, African, Latino, and mixed population), duration (acute, chronic, patients including both acute and chronic SZ, and not mentioned about either chronic or acute), measurement time (before drugs using and after drugs using), gender (male and female) and age (<50 years old and >50 years old) were performed, respectively. Power analysis to detect the reliability of the meta-analyses' results was performed by software Power and Precision V4. Power analysis was set that the P value of the power larger than 80% is acceptable level of detecting a real effect (or a 20% probability of making a Type II error) (Ellis, 2010). Publication bias was measured by funnel plot and Egger's test (Egger et al., 1997).

3. Results

3.1. Identified publications and characteristics of studies

Through databases searching, 467 records were yielded. After removing the duplicated records, 273 records were left. Then, the records were screened by titles and abstracts, 68 records were selected for further assessment. Forty-two publications were excluded in full-test evaluation (Supplement table S1). At last, 26 publications (26 studies) were included in the meta-analysis (Fig. 1).

Table 1 presents the characteristics of the included publications. All the study design was case-control study except one study (Ayesa-Arriola et al., 2012) was cross-sectional in this meta-analysis. There were 20 publications written in English, 1 in Turkish, 1 in French, and 4 in Chinese. Ethnicity was defined as five groups: Caucasians, Asians, Africans, Latinos, and mixed population. According duration of the disease, the SZ cases were defined as four groups: (1) acute SZ, (2) chronic SZ, (3) both, the patients including both chronic and acute patients; (4) NM, not mentioned about either chronic or acute. Measurement time was defined as four groups: (1) before drugs using was that SZ patients was naive to antipsychotics or had been withdrawn from these medications for at least two weeks; (2) after drug using was that the measurement after antipsychotics had been used; (3) mixed, the indexes were measured patients either before or after the drugs were used; (4) NM, not mentioned about either before or after the drugs used.