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Meta-analysis of the Relationship Between Plasma Homocysteine Levels and Carbamazepine Monotherapy in Patients with Epilepsy

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Abstract

Background: Numerous studies have shown that long- term treatment with anticonvulsants may be an important risk factor for the onset of atherosclerosis, or worsening of its symptoms.
Context: The present study aimed at investigating the relationship between carbamazepine (CBZ) monotherapy and plasma homocysteine (Hcy) levels in patients with epilepsy.
Evidence Acquisition: Studies concerning homocysteine levels in carbamazepine monotherapy patients with epilepsy, which were published in VIP, Wanfang, CNKI, Cochrance Library, PubMed, Web of Science, and EMBASE, were included in March 2016. The quality of the controlled clinical trials (CCT) selected for this study was assessed using the Newcastle-Ottawa scale (NOS), and the relevant data of the included studies were extracted through RevMan5.2 software.
Results: In this meta-analysis, 22 eligible studies were enrolled including 9 Chinese and 13 English studies. The study included a total of 1604 cases including 575 cases of patient group and 1029 control group cases. Results of the meta-analysis showed that plasma homocysteine level in patients with epilepsy with long- term treatment of CBZ was significantly higher than that in the healthy control group [SMD = 1.55, 95% CI: [1.09, 2.01], $P < 0.00001$]. Moreover, there was significant heterogeneity in the estimates according to I2 test ($P < 0.00001$; $I^2 = 93\%$). Further subgroup analysis showed that no significant difference was present when the study participants were grouped by region and age, however, the risk of heterogeneity in the West Asian group (I2 = 58%, P = 0.07) was diminished when compared with overall groups (I2 = 93%, $P < 0.00001$). The results of sensitivity analysis by Stata12.0 showed good stability. The funnel plot method and Begg method were used to detect publication bias, and the results showed a substantially symmetrical funnel plot, $Pr > |Z| = 0.091 > 0.05$ (no statistical significance), suggesting no significant publication bias in the study. Loss factor of safety (Nfs) 0.05 equaled 7269.16 (P = 0.05), meaning that addition of about 7269 negative results were required to overthrow the conclusion of this study.
Conclusions: The seizures significantly increased plasma homocysteine levels in the patients, thus it is appropriate to add folic acid, vitamin B12, and vitamin B6 to reduce the seizures. Moreover, homocysteine may be beneficial for those patients with epilepsy who take carbamazepine.

Keywords: Epilepsy, Carbamazepine, Homocysteine, Meta-Analysis

1. Background

Epilepsy is a clinical syndrome with transient brain dysfunction, which is caused by sudden and abnormal discharges of brain neurons, induced by a variety of reasons. This syndrome is common in clinical neurological diseases, with the characteristics of high incidence, long duration, and easy relapse, etc. The global number of epileptic patients is about 50 million; the domestic epidemiological data show that the clinical prevalence of epilepsy is about 7% and the incidence is about 25,100,000 to 45,100,000. There are about 10 million patients with epilepsy in China, and the number is increasing at the rate of 450,000 per year (1). Sener et al. (2) found that epilepsy itself will not increase the homocysteine level. However, a current study found that long-term treatment of antiepileptic drugs would cause metabolic abnormalities in patients, causing the increase of homocysteine (Hcy) concentration (3), and they further indicated that about 10% to 40% of patients with epilepsy might have hyperhomocysteine (Hhcy) (4) concurrently. Eikelboom et al. (5) showed that Hhcy caused vascular endothelial dysfunction, thrombosis, cholesterol, disorder of triglyceride synthesis and metabolism, and the activation of monocytes, which all can contribute to sclerosing disease including the occurrence and progression of glomerulosclerosis. In the recent years, Hhcy has been considered as an independent risk factor for diseases (6) such as atherosclerosis,

cardiovascular, and cerebrovascular diseases. Therefore, antiepileptic drugs may be one of the causes to increase the risk of the occurrence of these diseases. Antiepileptic drugs are now widely used by patients with epilepsy. As one of the first-line antiepileptic drugs, carbamazepine is the first choice and most commonly used in curing complex partial seizures (7). There is controversy about the effect of carbamazepine (CBZ) on the level of Hcy, and there are few related studies on this topic in the world. The underling mechanism is not clear, so further studies are needed to reach a more accurate and comprehensive conclusion. Here, we, used meta-analysis to investigate the relationship between carbamazepine monotherapy and plasma homocysteine levels to provide the basis for clinical rational drug use.

2. Methods

2.1. Search Strategy

We retrieved studies from databases of VIP, Wanfang Database, CNKI and Cochrance Library, National Library of Medicine (PubMed), Chinese Science Citation Database (Web of Science), Excerpta Medica Database (EMBASE) and other databases in March 2016. We used the words "carbamazepine", "homocysteine", "epilepsy", and "epilep*" as search terms. We also looked up the bibliographies of the retrieved literatures one by one to find eligible studies. The language of the literatures was limited to Chinese and English.

2.2. Inclusion and Exclusion Criteria and Outcome Indicator

Inclusion Criteria were as follow: (1) controlled clinical trial studies; (2) the patient group consisting of patients with epilepsy who received carbamazepine monotherapy, while the control group consisted of healthy volunteers not taking antiepileptic drugs; and (3) only Chinese and English studies were included in the study. Exclusion Criteria were as follow: (1) non-clinical trial studies; (2) non-rigorous experimental design such as significant proportion imbalance between the patient group and the control group; (3) studies with incomplete summarization and data as well as repeated data; and (4) patients with congenital metabolic defects of Hcy, folic acid, and vitamin B; (5) patients with hypertension, diabetes, coronary heart disease, stroke, liver and kidney diseases, etc.; (6) those taking B vitamins as adjunctive drugs in drug treatment process; (7) smokers, long-term alcoholics and vegetarians; (8) those with tumor and recent surgery trauma;(9) patients with peripheral vascular disease or peripheral vascular embolism diseases and endocrine diseases such as hypothyroidism; (10) patients with mental illnesses such as depression and schizophrenia; and (11) those who were taking thiazide diuretics or azathioprine and other similar drugs (8). Interventions: The patient group consisted of epileptic patients receiving carbamazepine monotherapy, while the control group consisted of healthy individuals who received no pharmacological intervention. Outcome Indicator: The plasma homocysteine levels in patients with epilepsy receiving carbamazepine monotherapy or the healthy group without pharmacological intervention in the same period; the core data were continuous variables [presented as mean $\pm$ standard deviation].

2.3. Data Screening and Quality Evaluation

2.3.1. Data Screening

Two independent researchers separately screened the studies according to the inclusion and exclusion criteria. (1) Initial Screening: previewing the title and abstract of the studies; excluding those that did not match the research content; summarization; animal or in vitro trials; report of adverse reactions; repeatability and so on.; (2) reading the full text of the studies that might have been qualified to be included in the study and analyzing them one by one to determine whether they met the inclusion criteri; (3) Objection Handling: for any objection or disagreements arising in the screening process, the 2 researchers held discussion.

2.3.2. Quality Evaluation

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of each eligible article including the appropriateness of the case, the representativeness of the case, the selection of the control, and the determination of the control. The same method was used by the 2 researchers to determine the exposure factors of the patient group and control group, and the no response rate. The quality evaluation criteria were as follow: (1) the section of the patient group and the healthy control group had the highest score of 4 points; (2) the comparability of the patient group and the control control group had the highest score of 2 points; and (3) the exposure factor measurement had the highest score of 3 points. The highest total score was 9 points; those studies with $>$ 6 points were of high-quality studies. If there were any disagreements, the 2 researchers settled them through discussion.

2.4. Data Extraction

Two researchers independently extracted and recorded the relevant data; if there was any disagreement, the 2 researchers would have reached a consensus before extraction. The data presented included the first author, time of publication, the region of the study, the

information of the patient group, and the control group (carbamazepine dose and duration of treatment, number of participants, and the plasma homocysteine levels of the 2 groups).

2.5. Statistical Analysis

Statistical analysis was performed using RevMan 5.2 software based on the data provided in the eligible studies. The heterogeneity test of the findings was performed using χ^2 test and I^2 test. When I2<50%, it presents homogeneity in each study, and thus the fixed-effect model should be used for combined statistical analysis; when $I^2 \geq 50\%$, it indicates that there is heterogeneity among the studies, and the random-effect model shall be used for statistical analysis. The measuring results of this study are continuous variables, which calculated the standardized mean difference (SMD) and 95% confidence interval (95% CI) to create the forest plot. If there is heterogeneity risk, sensitivity analysis and other methods shall be employed to analyze the causes of heterogeneity, and the subgroup analysis should be undertaken. We used funnel plot method, Begg method, or Fail-safe number to conduct publication bias analysis on the Meta-analysis.

3. Results

3.1. Literature Retrieval Results

According to the retrieval strategy (Figure 1), we retrieved 722 Chinese and English studies including 94 Chinese (67 from CNKI, 16 from VIP, and 11 from Wanfang) and 628 English studies (120 from PubMed, 75 from Web of Science, and 433 from EMBASE). There were 657 studies left after excluding the duplicate articles. After rejecting those that did not meet the inclusion criteria, 79 studies were left. Eventually, by reading their full texts, we selected 22 studies (9 in Chinese and 13 in English). See Table 1 for the basic parameter data included in the study.

3.2. Basic Features Included in the Study

We included 22 eligible studies in total, all of which were cohort studies containing 1,604 study participants, among which there were 575 patient groups and 1,029 healthy control groups. After conducting Newcastle-Ottawa quality evaluation on the included studies, we found that 10 of the studies scored 7 points in the quality evaluation and 12 scored 6 points.

3.3. Meta-analysis Results

3.3.1. Heterogeneity Test

A heterogeneity test was performed among the 22 studies included in the final study. Heterogeneity among each clinical trial was $I^2 = 93\%$, $P < 0.00001$, which was statistically analyzed using the random-effect model. The results revealed that the overall difference was statistically significant. The plasma homocysteine level of the patient group receiving carbamazepine monotherapy was higher than that of the healthy control group (overall effect SMD = 1.55, 95%, CI: [1.09, 2.01], $P < 0.00001$; Figure 2). The results of the analysis were different. Heterogeneity existed among various studies, thus it is necessary to conduct subgroup analysis to explore the source of heterogeneity.

3.3.2. Subgroup Analysis

The studies were divided into 4 subgroups (Figure 3) according to regional difference including Europe, North Africa, West Asia and East Asia. They could also be divided into 2 subgroups according to age difference of the participants; namely, < 18-year-old and ≥ 18-year-old (Figure 4). Subgroup analysis revealed a lower risk of heterogeneity in the West Asian group ($I^2 = 58\%$, $P = 0.07$) than in the overall groups ($I^2 = 93\%$, $P < 0.00001$) (Table 2).

3.3.3. Sensitivity Analysis

We used Stata12.0 to perform sensitivity analysis to evaluate the stability of the meta-analysis. The results revealed that all study results were between the ceiling and floor, in other words, the overall trend of the SMD of the study was consistent with good stability (Figure 5).

3.3.4. Publication Bias Analysis

There are many methods to evaluate publication bias in the meta-analysis. The funnel plot method is a commonly used bias detection method. In this study, the funnel plot is plotted with the standard mean difference as abscissa and standard error as ordinate (Figure 6). The results showed that the funnel diagram is basically symmetrical. The Stata 12.0 Software was used for Begg test, the results of which showed the Pr > = 0.091 > 0.05, which indicated that the results were not statistically significant, and suggesting no significant publication bias in the study.

3.3.5. Fail-safe Number Analysis

When the results of the meta-analysis are statistically significant, the analysis on fail-safe number is used to calculate the minimum number of studies with negative results that is enough to overthrow the conclusion of the meta-analysis and to eliminate the possibility of bias. The greater the fail-safe number, the more stable the results of the meta-analysis, and the less likely the meta-analysis is biased (29). In this study, the fail-safe number (Nfs) (30) 0.05 is 7269.16 (P = 0.05), which needs about 7,269 negative results to overthrow this conclusion that plasma ho-

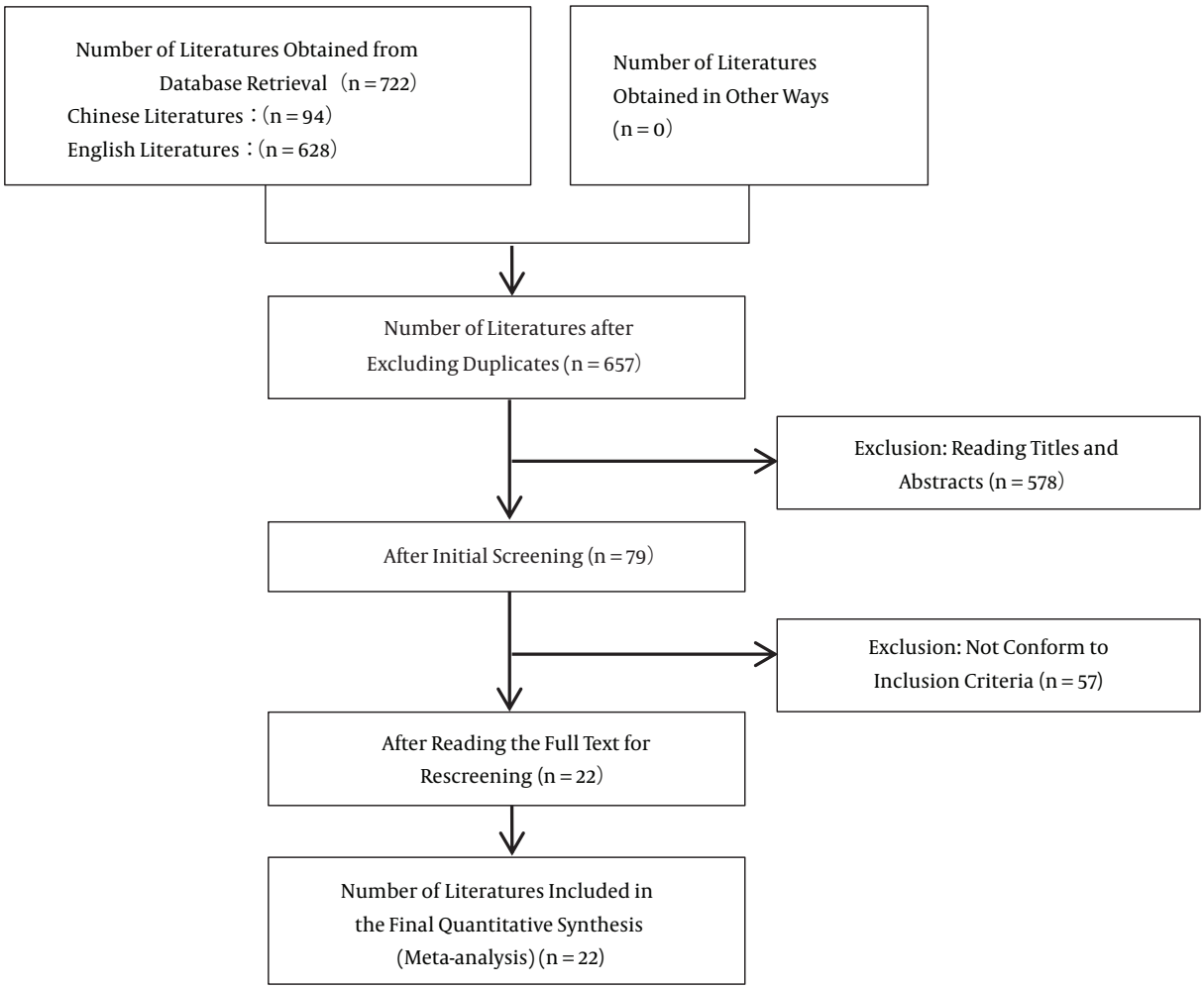

Figure 1. Flowchart Depicts the Process of Selection of Studies to be Included in This Analysis

mocysteine levels of patients who received carbamazepine monotherapy significantly increased.

4. Discussion

Epilepsy is mainly treated by drug therapy. A vast majority of patients with epilepsy need long-term or even lifelong treatment of antiepileptic drugs to control seizures. However, recent studies have found that long-term use of antiepileptic drugs could induce metabolic abnormalities in patients, leading to elevated Hcy concentration (3). Homocysteine is a non-essential amino acid containing sulfenyl, which is an important intermediate in the metabolic processes of methionine and cysteine. It has been found that homocysteine can damage the vascular endothelial cells, resulting in the dysfunction of cell selective permeability, the deposition of cholesterol and triglycerides in the vascular wall, the proliferation of smooth muscle cell, inhibition of cellular NO synthesis, promotion of cellular NO degradation, and the spasm of vascular smooth muscle. It will also affect the platelet aggregated coagulation factors' activity through the promotion of thromboxane and prostacyclin formation, thereby promoting the occurrence of atherosclerosis and thrombosis formation, leading to cardiovascular and cerebrovascular diseases (31, 32). Moreover, Gu (33) and Castro et al. (34) found that plasma Hcy level was the main risk factor of atherosclerosis and cardiovascular diseases. As a first-line antiepileptic drug, carbamazepine is widely used to control various types of epileptic seizures, and thus long-term use of carbamazepine by patients with epilepsy may be one of the important risk factors of atherosclerosis and cardio-

Table 1. Basic Parameter Data Included in the Study

Study	Year	Ethnicity	Duration	CBZ Group			Control Group	
				Dose	N	Hcy, μmol/L	N	Hcy, μmol/L
Schwaninger et al. (9)	1999	European	$\geq$ 1 mo	Unknown	15	21.7 $\pm$ 9.6	35	9.5 $\pm$ 0.5
Verrotti et al. (10)	2000	European	After 1 y	Unknown	28	14.1 $\pm$ 8.1	63	7.9 $\pm$ 4.5
Apeland et al. (11)	2001	European	6 mo	Unknown	42	13.8 $\pm$ 1.6	42	9.3 $\pm$ 0.4
Achilleas et al. (12)	2006	European	20 w	unknown	20	7.6 $\pm$ 1.7	172	6.4 $\pm$ 1.6
Kurul et al. (13)	2007	West-Asian	> 1 y	unknown	11	8.13 $\pm$ 5.28	10	7.66 $\pm$ 2.34
Vurucu et al. (14)	2008	West-Asian	$\geq$ 6 mo	unknown	29	6.38 $\pm$ 1.73	62	5.52 $\pm$ 2.53
Mintzer et al. (15)	2009	European	6 mo	Unknown	15	11.1 $\pm$ 4.2	16	11.5 $\pm$ 5.3
Chuang et al. (16)	2011	East-Asian	> 2 y	Unknown	41	13.31 $\pm$ 8.41	60	9.41 $\pm$ 2.65
El-Farahaty et al. (17)	2014	North-Africa	> 2 y	10-17 mg/kg/d	14	8.63 $\pm$ 2.99	34	2.7 $\pm$ 0.5
Karabiber (3)	2002	West-Asian	> 12 mo	Unknown	30	16.0 $\pm$ 13.1	29	9.2 $\pm$ 2.7
Yoo and Yung (18)	1999	East-Asian	< 5 y	Unknown	23	12.7 $\pm$ 1.7	103	7.9 $\pm$ 1.2
Sener et al. (2)	2005	West-Asian	2 y	Unknown	19	19.6 $\pm$ 21.4	11	11.5 $\pm$ 11.4
Eldeen et al. (19)	2012	North-Africa	1 y	Unknown	8	5.5 $\pm$ 1.9	30	5.5 $\pm$ 1.4
Xia (20)	2012	East-Asian	6 mo	0.6g/d	35	11.31 $\pm$ 2.66	74	9.79 $\pm$ 2.23
Li et al. (21)	2013	East-Asian	> 1 y	Unknown	40	10.005 $\pm$ 2.9494	40	6.755 $\pm$ 1.5726
Liu et al. (22)	2012	East-Asian	2 mo	0.3 g/d	45	24.5 $\pm$ 5.9	50	10.0 $\pm$ 4.0
Ming (23)	2014	East-Asian	One Course	Unknown	32	21.92 $\pm$ 11.54	32	12.74 $\pm$ 5.29
Xuefeng (24)	2012	East-Asian	5 mo ~ 3 y	Unknown	19	13.56 $\pm$ 4.34	40	6.56 $\pm$ 2.11
Wang et al. (25)	2007	East-Asian	2 mo ~ 13 y	Unknown	30	21.1 $\pm$ 6.4	40	10.20 $\pm$ 4.3
Caizhi et al. (26)	2008	East-Asian	2 mo ~ 4.5 y	Unknown	31	12.78 $\pm$ 3.06	36	6.17 $\pm$ 1.34
Zhang (27)	2013	East-Asian	$\geq$ 32 w	Unknown	23	22.64 $\pm$ 10.45	20	10.30 $\pm$ 4.43
Shan et al. (28)	2014	East-Asian	1 mo	Unknown	25	20.77 $\pm$ 5.23	30	10.47 $\pm$ 2.43

Table 2. Subgroup Analysis Results Included in the Study

Subgroup	Number of Study	Standardized Mean Difference	95%CI	Heterogeneity Test, %	P Value
Ethnicity					
European	5	4.12	1.61 - 6.62	94	< 0.00001
West-Asian	11	7.41	5.30 - 9.52	58	0.07
East-Asian	4	2.34	-0.51 - 5.18	95	< 0.00001
North-Africa	2	2.95	-2.86 - 8.77	97	< 0.00001
Age, y					
< 18	8	3.45	1.34 - 5.55	94	< 0.00001
$\geq$ 18	14	6.78	5.12 - 8.44	94	< 0.00001

vascular diseases.

Vitamin B12, vitamin B6, and folic acid are cofactors in the process of homocysteine metabolism. It is generally assumed that Hcy level and blood vitamin B12, vitamin B6 and folic acid levels were negatively correlated in nonlinearity, which means lower concentration of vitamin B12, vitamin B6, and folic acid caused higher homocysteine in serum (35). Consuelo et al. (36) found that taking a very low dose of folic acid caused a significant decrease in the plasma Hcy level of patients with epilepsy who had a

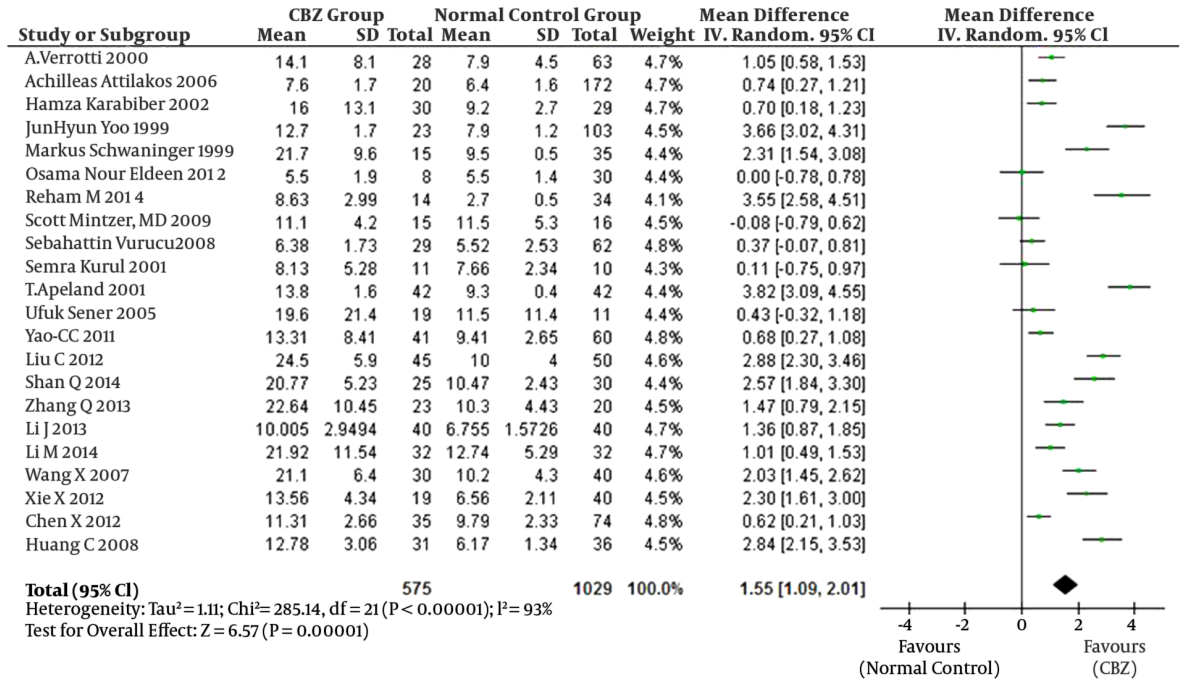

Figure 2. Forest Plot of Changes of Plasma Homocysteine Levels in Patients with Epilepsy Receiving Carbamazepine Monotherapy

history of long-term use of antiepileptic drugs. However, some studies found no effect of carbamazepine monotherapy on folate levels (11, 37). Tumer et al. (38) found that the mechanism of function of carbamazepine was different from enzyme-induced antiepileptic drugs which induce liver enzymes to accelerate the metabolism of folic acid. Instead, it interferes with intestinal folate absorption or directly affects the function of coenzyme in the process of folic acid metabolism, resulting in folic acid level decrease. Michael Linnebak et al. (39) have indicated that by appropriate oral intake of vitamin B12, vitamin B6, and folic acid and reducing methionine in diet, the blood Hcy level can be decreased.

Heterogeneity evaluation is a must in meta-analysis, which is of great importance to ensure the quality of meta-analysis (40). In the present study, heterogeneity analysis was performed using sensitivity analysis and subgroup analysis. The subgroup analysis based on the differences in age and region of the population revealed a lower heterogeneity risk in the West Asian group than in the overall population. The differences of vitamin B12, vitamin B6, and folic acid intake of people between different regions may be important factors in influencing the plasma Hcy level; however, a more accurate and comprehensive conclusion shall be further studied. Publication bias is one of the important factors affecting the quality of meta-analysis. There are many methods to evaluate publication bias in meta-analysis including funnel plot method, Begg method, Egger method, trim method, fail-safe number method, and so on. Currently, the most commonly used bias detection methods are funnel plot method and fail-safe number method, but these 2 methods cannot make quantitative detection on publication bias, while the Begg method and Egger method can be used to quantify the bias (29). In addition, considering the fact that the funnel plot method can only be fully effective when the number of studies is large and that the study only included 22 studies, the application of funnel plot was limited to a large extend (41). Therefore, the Begg method was used for quantify detection.

This study showed that plasma homocysteine levels in patients with epilepsy, who received carbamazepine monotherapy for long periods ($\geq$ 1 month), were significantly higher than that in the healthy control group. To reduce the risk of carbamazepine-induced hyperhomocysteinemia, it is recommended that patients with long-term use of carbamazepine monitor their blood homocysteine levels regularly for early detection and intervention. Once an increase in Hcy level is found, appropriate folic acid, vitamin B12, and vitamin B6 supplements are necessary

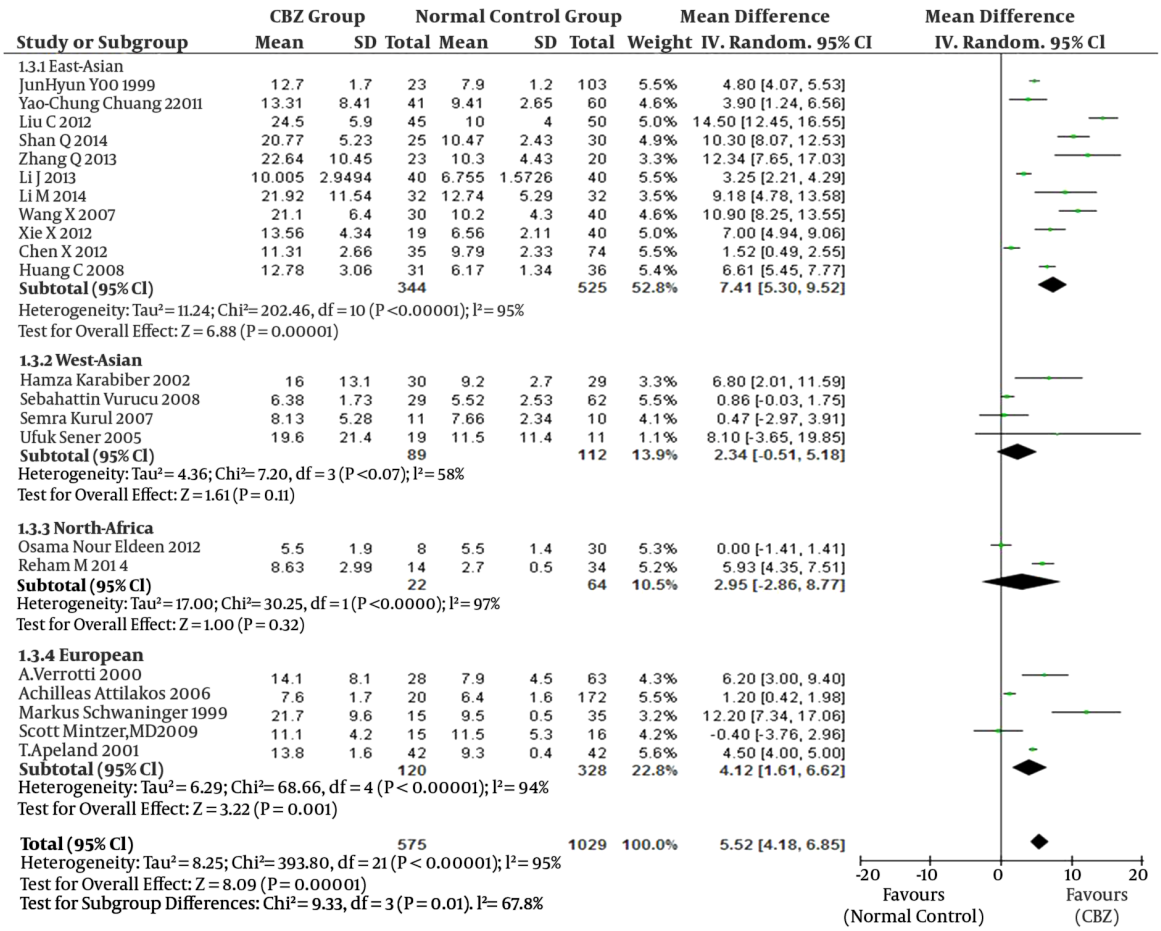

Figure 3. Subgroups Grouped by Regions of the Studies

to reduce homocysteine level, which may be beneficial for those patients with epilepsy who take carbamazepine. However, because of the mere inclusion of published Chinese and English studies, the large difference of treatments among the groups, the unclear carbamazepine dosage, and other limitations, a more reliable and comprehensive conclusion needs to be verified based on more high-quality studies with larger sample sizes.

Footnotes

Competing Interests: The authors declare that they have no competing interests.

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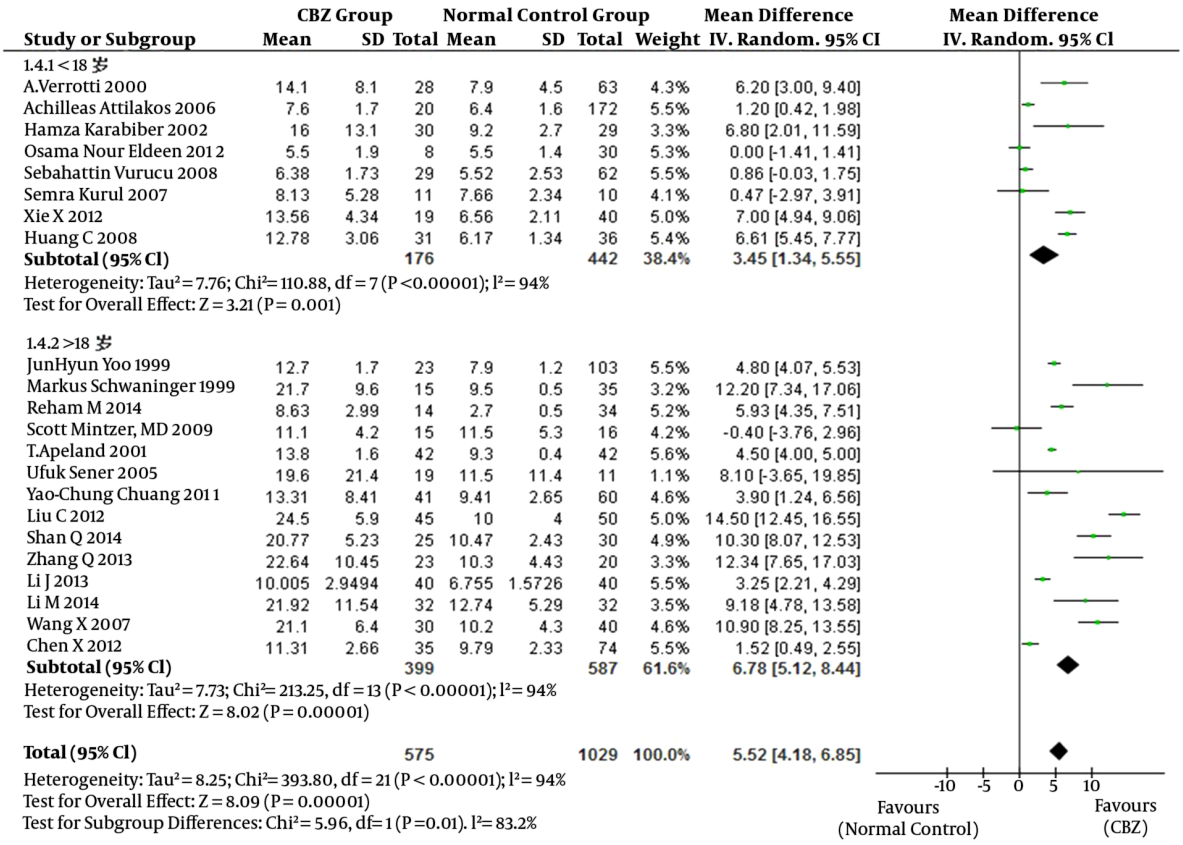

Figure 4. Subgroups Grouped by Age of the Subjects

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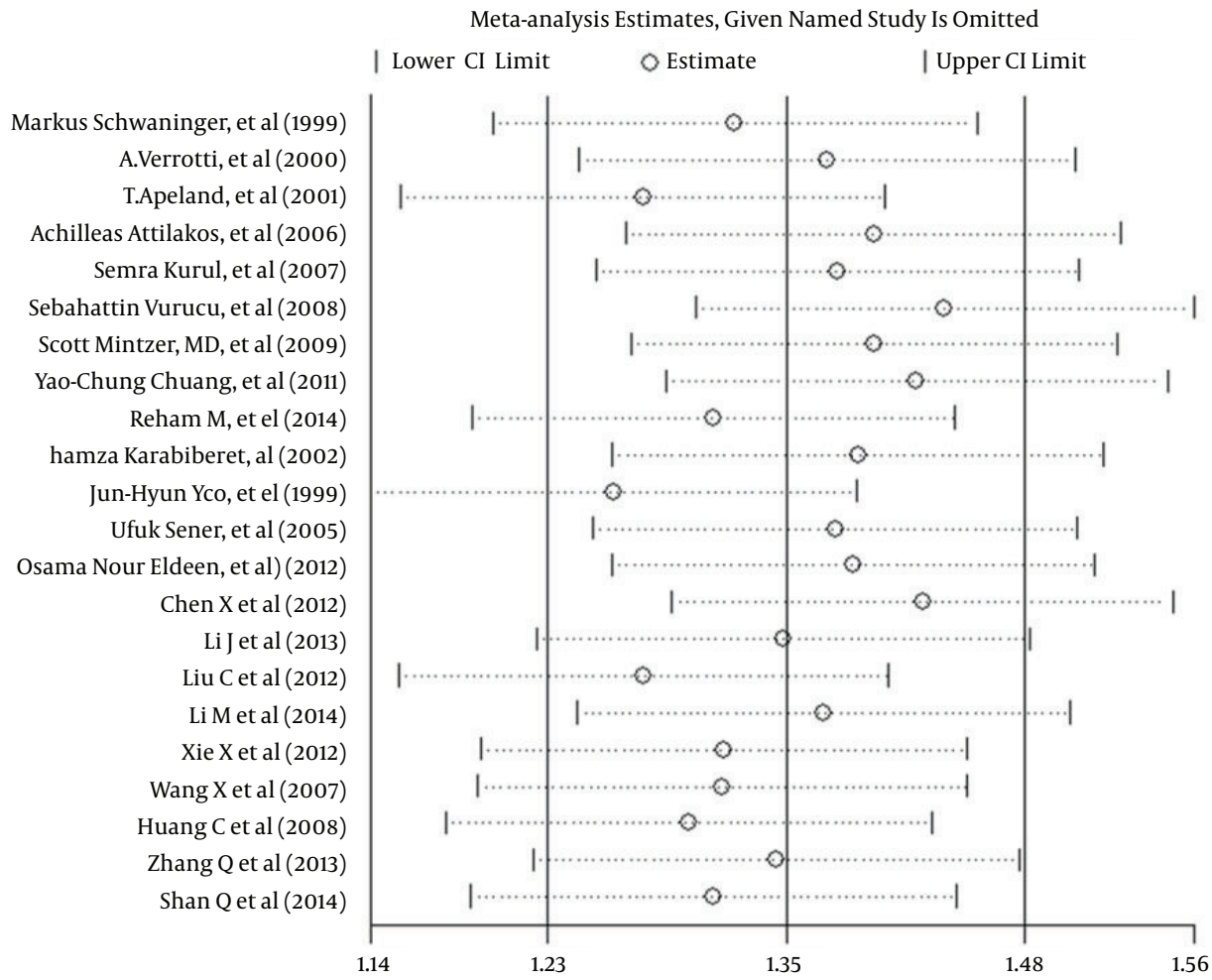

Figure 5. Sensitivity Analysis

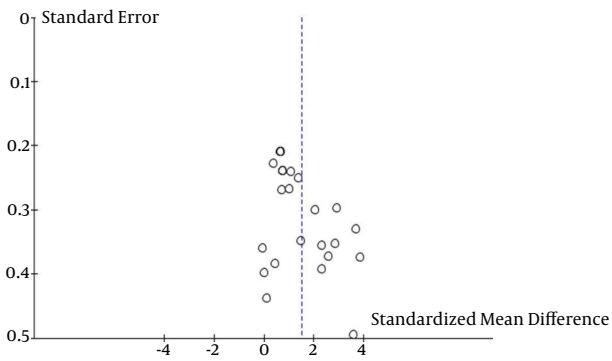

Figure 6. Funnel Plot

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