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*Original Article*

# Meta-analysis of plasma homocysteine content and cognitive function in elderly patients with Alzheimer's disease and vascular dementia

Beiyun Wang, Yuan Zhong, Hong Yan, Liang Cui

*Department of Geriatrics, Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai 200233, China*

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**Abstract:** Objective: To evaluate the relationship between homocysteine and cognitive function of Alzheimer's disease (AD) patients and vascular dementia (VD) patients. Methods: By Cochrane system evaluation we retrieved relevant publications from MEDLINE, Embase, OVID, controlled clinical trial database of the Cochrane library and others. Two evaluators jointly assessed the research quality of the retrieved publications and carried out meta-analysis on the homogeneous study. Results: MMSE score in the AD group was lower than that in normal control group (MD = -11.98, 95% CI (-13.30, -10.65)), and the homocysteine content was higher than that in the normal control group (MD = 2.72, 95% CI (1.79, 3.64)), with a statistical difference between the two groups ($P < 0.05$). The homocysteine content in the AD group was higher than that in the VD group (MD = -4.76, 95% CI (-7.59, -1.93), $P < 0.05$). Conclusions: MSE score and homocysteine content can be used as useful indicators to distinguish AD and normal subjects; homocysteine content can be used as an indicator to differentiate AD from VD. Clinically, more randomized controlled trials are needed to test and verify the relationship in cognitive function between homocysteine and AD and VD.

**Keywords:** Alzheimer's disease, homocysteine, cognitive function, elderly people, meta analysis

## Introduction

Alzheimer's disease (AD), or senile dementia, is the most prevalent form of dementia, but its cause still remains unknown. The prevalence of AD increases with age due to increased life expectancy and consequently the growing population of the elderly. It has been predicted that by 2050, 1 in 85 people will suffer from AD globally [1]. As the global population is aging, AD poses a severe threat to the health of the elderly, compromising the quality of their lives and inflicting a heavy burden on the patients, their families and the society. AD is now the fourth leading cause of elderly death following carcinoma, heart disease and cerebrovascular disease.

AD patients exhibit progressive degeneration of the nervous system with a marked decrease in the number of neurons, especially in the hippocampus, formation of neurofibrillary tangles (NFT) in neurons and appearance of a large number of senile plaques (SP) between neurons. Clinically, AD mainly manifests as progressive loss of memory and cognition, speech disorder, and psychomotor abnormalities. Homocysteine is an important intermediate product of methionine metabolism *in vivo*. Numerous studies have shown that hyperhomocysteinmia plays an important role in the pathogenesis of artherosclerosis and thromboembolic disease, which has been considered as one of the independent risk factors for AD [2-4]. Another study [5] showed that abnormal elevation of homocysteine may cause damage to the nervous system. A prospective study by Swshadri *et al*. [6] of 1092 volunteers with a mean age of 76 years indicated that hyperhomocysteinemia was an important independent risk factor for AD. When plasma homocysteine level exceeds 14 μmol/L, the risk of suffering from AD is doubled; when plasma homocysteine level increases 5 μmol/L, the risk of suffering from AD increases 40%.

In this meta-analysis, we analyzed differences in plasma homocysteine levels between AD patients, vascular dementia patients and normal subjects so as to provide a reference for clinical decision.

## Methods

### *Study objects*

Related documents published as of May 2013 on plasm homocysteine levels in elderly AD patients.

### *Literature retrieval*

The electronic databases of PubMed, MEDLINE, EMBASE, CCTR, CNKI, CBM, WanFang DATA, VIP database, and Google Scholar were search from database start date to May, 2013. Two of the authors (BW and YZ) independently screened the titles and abstracts of the studies from the electronic search to identify all citations potentially containing the comparison of interest. They independently evaluated and identified these studies by searching references and abstracts from meetings to determine the final set of included articles. Disagreements were resolved by discussion and by further discussion with an independent colleague if necessary. Publications in Chinese and English were retrieved.

Chinese Biomedical Literature (CBM): Retrieval field: Default field (including Chinese titles, abstracts, authors, subject terms, feature words, keywords, and journal titles).

Retrieval conditions: (default: Alzheimer's disease or AD) and (default: homocysteine) and (default: cognitive function) and (default: elderly).

PubMed: Retrieval conditions: (Randomized Controlled Trial [ptyp] OR (Clinical Trial [ptyp]) AND ((“Alzheimer disease” [All Fields] AND “Homocysteine” [All Fields]) AND (“Cognitive function” [All Fields]) AND (“The old” [All Fields]) AND (English [lang] OR Chinese [lang])).

Chinese Text CNKI-China Journal Net: Retrieval conditions: ((key word = Alzheimer's disease) and (key word = homocysteine)) and (key word = cognitive function) and (key word = elderly).

### *Literature screening*

Literature inclusion criteria: (1) documents were published one time; (2) the experimental design was randomized controlled trials; (3) studies were carried out or published; (4) the size of the sample was clearly stipulated; (5) clear diagnostic criteria for cases were provided; (6) Study subjects were patients with AD or vascular dementia; (7) the publication described the comparison of MMSE scores and homocysteine levels, etc.; (8) the methods of data collection were scientific; (9) the methods of data analysis were correct.

Exclusion criteria: (1) studies that did not provide the sources of cases and controls, nontherapeutic clinical study, animal experiment, studies that were not based on original data, and studies with no clear grouping numbers; (2) unclear diagnostic criteria for cases; (3) age < 60 years; (4) methods of data collection were unscientific; (5) literature review; (6) methods of data analysis were erroneous or not provided; (7) repeated publication; (8) retrospective analysis.

### *Literature evaluation and data extraction and analysis*

Two of the authors (BW and YZ) made evaluations separately and independently in terms of the following aspects: (1) general data: the first author of the document, publication year, the source, the publication date and others; (2) the design proposals for various studies; (3) the number of samples (patients), characteristics and treatment results included in various documents; (4) study outcome.

### *Statistical analysis*

Meta-analysis was done using RevMan5.0 software. For dichotomous data, relative risk (RR) was used, and the 95% confidence interval (CI) was also indicated. For continuous data, standardized weighted mean difference (SMD) was used, and the 95% CI was also indicated. We considered a $p$-value of less than or equal to 0.05 to be statistically significant. Heterogeneity across the studies was tested using the $I^2$ statistic, which quantitatively measures the degree of inconsistency across studies. Studies with an $I^2$ statistic of < 25%, ~50%, ~75%, and ~100% were considered to have no, low, moderate, and high heterogeneity, respectively [7]. A fixed-effects model (Mantel-Haenszel method) [8] was used when significant heterogeneity was not present, whereas a random-effects model (DerSimonian-Laird method) [9] was used when significant heterogeneity existed ($I^2$ > 10%).

**Table 1.** Basic characteristics of the included studies

| Authors | Journals | Pub Year | Number | | | Sex (M/F) | | | Mean age ± SD (years) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | AD | VD | Con | AD | VD | Con | AD | VD | Con |
| Bottiglieri T | Mech Ageing Dev | 2001 | 48 | 7 | 22 | 16/32 | 4/3 | 7/15 | 71.0 ± 8.5 | 72.9 ± 6.2 | 75.6 ± 6.2 |
| Clarke R | Arch Neurol | 1998 | 164 | | 108 | 64/100 | | 46/62 | 73.2 ± 8.6 | | 72.8 ± 8.8 |
| Folin M | Biogerontology | 2005 | 79 | 13 | 24 | | NA | | 80.33 ± 7.06 | 82.46 ± 4.75 | 71.24 ± 9.69 |
| Hogervorst E | Arch Neurol | 2002 | 137 | | 277 | 55/82 | | 138/139 | 73.9 ± 9.0 | | 73.3 ± 7.7 |
| Koaseoglu E | Clin Biochem | 2007 | 51 | 67 | 40 | 21/30 | 42/25 | 17/23 | 78.25 ± 4.14 | 80.0 ± 4.79 | 76.13 ± 3.88 |
| Miller JW | Neurology | 2002 | 32 | 15 | 22 | 13/19 | 9/6 | 8/14 | 78 ± 7 | 76 ± 5 | 75 ± 5 |
| Quadri P | Clin Chem Lab Med | 2005 | 111 | 25 | 79 | 37/74 | 11/14 | 29/50 | 78.9 ± 7.5 | 81.0 ± 5.2 | 75.0 ± 8.5 |
| Storey SG | J Gerontol | 2003 | 50 | 50 | 50 | 33/17 | 32/18 | 33/17 | 79 ± 10 | 78 ± 9 | 79 ± 9 |

AD: Alzheimer's disease; VD: vascular dementia; Con: control.

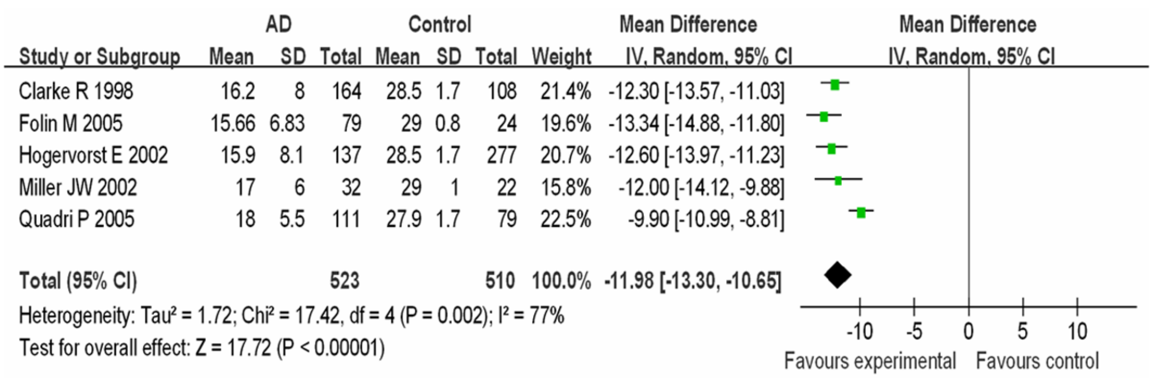


**Figure 1.** Forest plot showing MMSE scores of the Alzheimer's disease (AD) group and the control (Con) group.

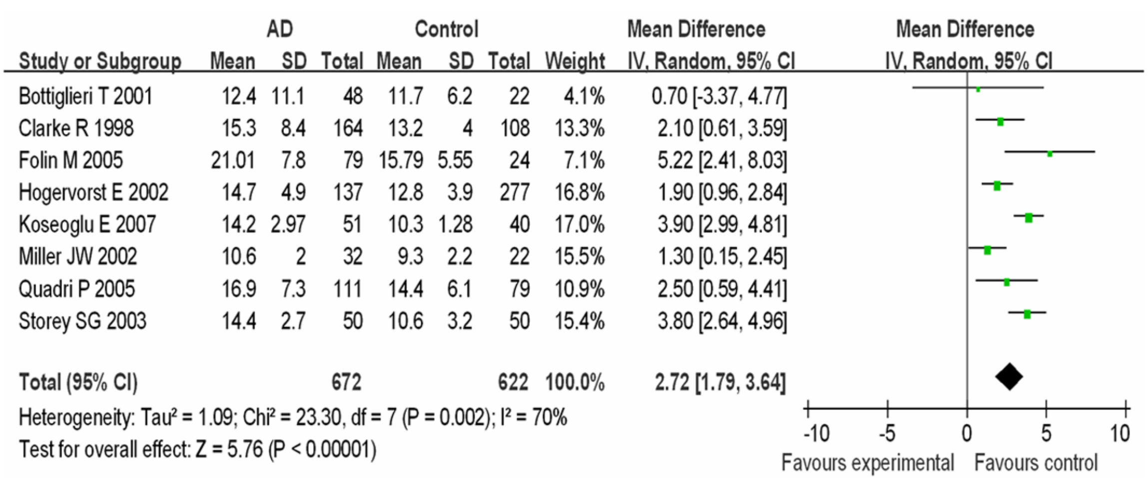


**Figure 2.** Forest plot showing homocysteine content of the AD group and the Con group.

## Results

### *Characteristics of included documents*

Preliminary screening of the retrieved documents yielded 119 publications. Twenty-four reviews, 70 non-clinical studies, and 7 retrospective analyses were excluded. Finally, 8 publications were included for the current meta-analysis [10-17].

### *Basic characteristics of the included studies*

Authors, journals that published papers, study time, the number of patients, gender, mean age and others of the included studies are listed in

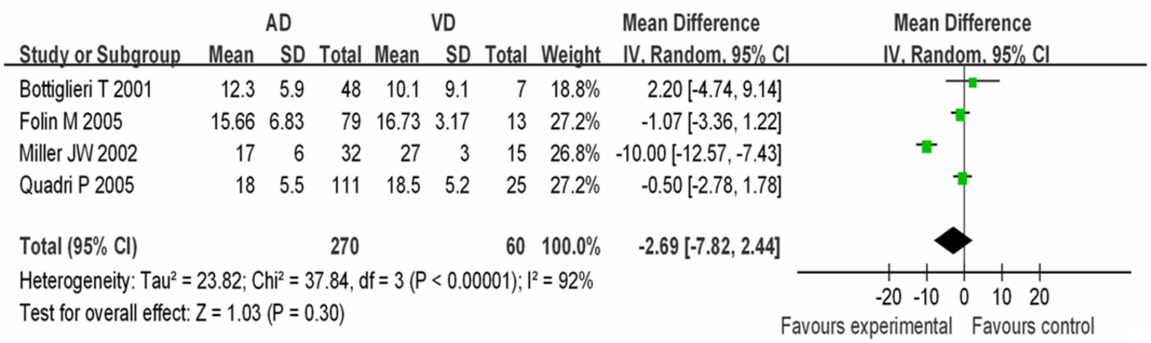


**Figure 3.** Forest plot showing MMSE scores of the AD group and the vascular dementia (VD) group.

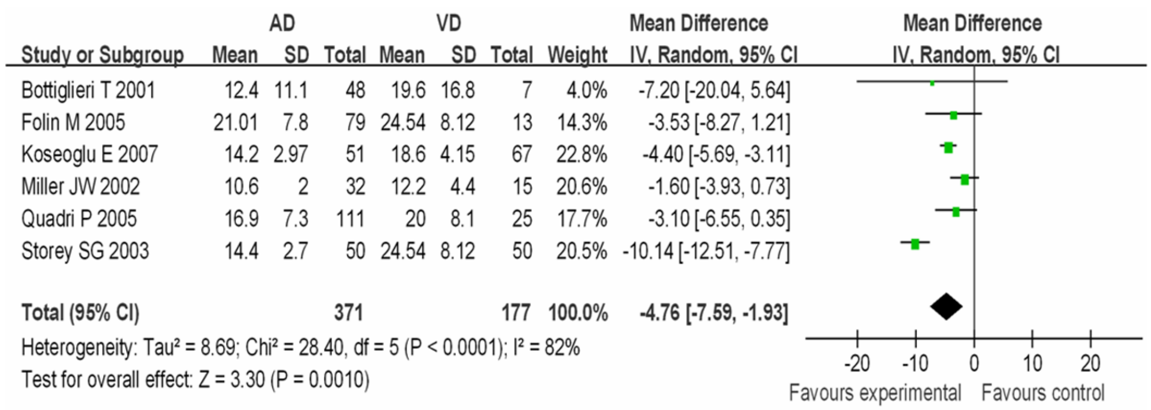


**Figure 4.** Forest plot showing homocysteine content of the AD group and the VD group.

**Table 1**. The included 8 publications covered totally 1471 persons. The largest number was 414 and the smallest 69 years. They included 672 AD patients, 177 vascular dementia patients and 622 normal subjects.

*Comparison of indicators in various groups*

*Comparison of MMSE scores between the AD group and the control group:* Five publications [10-14] studied and reported MMSE scores of the AD group and the control group. Upon examination, heterogeneity was found to exist between various studies (P = 0.002, $I^2$ = 77%), so random effects model was used. The result showed that the combined MD value was -11.98, 95% CI (-13.30, -10.65). Upon examination, the results were of statistical difference (Z = 17.72, P < 0.00001), indicating that the MMSE score of the AD group was lower than that of the control group (**Figure 1**).

*Comparison of homocysteine content between the AD group and control group:* Eight publications [10-17] studied and reported the result of homocysteine content between the AD group and the control group. Upon examination, heterogeneity was found to exist among various studies (P = 0.002, $I^2$ = 77%), so random effects model was used. The result showed that the combined MD value was 2.72, 95% CI (1.79, 3.64). Upon examination, the results were of statistical difference (Z = 5.76, P < 0.00001), indicating that homocysteine content of the AD group was higher than that of the control group (**Figure 2**).

*Comparison of MMSE scores between the AD group and the vascular dementia group:* Four publications [10-17] studied and reported the result of MMSE scores of the AD group and the vascular dementia group. Upon examination, heterogeneity was found to exist among various studies (P = 0.00001, $I^2$ = 92%), so random effects model was used. The result showed that the combined MD value was -2.69, 95% CI (-7.82, 2.44). Upon examination, the results were of statistical difference (Z = 1.03, P = 0.30), indicating that MMSE score of the AD group was not statistically different from that of the vascular dementia group (**Figure 3**).

*Comparison of homocysteine content between the AD group and the vascular dementia group:* Six publications [4, 10-15, 17] studied and reported the result of homocysteine content between the AD group and vascular dementia group. Upon examination, heterogeneity was found to exist among various studies ($P < 0.0001$, $I^2 = 82\%$), so random effects model was used. The result showed that combined MD value was -4.76, 95% CI (-7.59, -1.93). Upon examination, the results were of statistical difference ($Z = 3.30$, $P = 0.0010$), indicating that homocysteine content of the AD group was higher than that of the cascular dementia group (**Figure 4**).

## Discussion

Homocysteine is an intermediate product of methionine metabolism. Many studies showed that homocysteine was an independent risk factor for coronary artery disease, cerebrovascular disease, peripheral vascular disease and others. Some studies held that hyperhomocysteinemia played a role in the occurrence and development of AD. Studies have shown that high homocysteine caused cognitive function and resulted in AD, which may be associated with biochemical damage caused by oxidative stress [16]. High levels of homocysteine can markedly increase the content of oxygen free radicals and promote the formation of nitric oxide. High levels of nitric oxide can become neurotoxic substances [18]. Oxygen free radicals can promote schizolysis of APP (β amyloid protein precursor) and formation of Aβ amyloid protein, thus increasing the generation and deposition of Aβ, which is the main pathological change in AD.

Our study result showed that when the AD group was compared with the normal control group, the MMSE score was lower and the homocysteine content higher, with a statistically significant difference between the two groups ($P < 0.05$). When the AD group was compared with the vascular dementia group, the MMSE scores were not significantly different between the two groups ($P > 0.05$); the homocysteine content of the AD group was lower than that of the vascular dementia group, with a statistically significant difference ($P < 0.05$).

According to the comprehensive outcome from the above documents, it was generally considered that the MMSE score and homocysteine content could be used as one of the indicators to distinguish AD and normal elderly subjects, and the homocysteine content as one of the indicators to distinguish AD and vascular dementia.

The result of our meta-analysis was limited in the following aspects: firstly, although our study included 8 publications, we did not make stratified analysis on gender and different ages, so we could not see more detailed outcome; secondly, there existed selection bias that could not be excluded and the influence of confounding factors that could not be determined; furthermore, there existed methodological defects in publications included in our meta-analysis, such as not clearly explaining random method, blinding method and others, which affected our analysis results.

It is held in evidence-based medicine that the evidence obtained from randomized controlled clinical trials has the strongest authenticity and reliability; and the comprehensive conclusion is more convincing from systematic evaluation on multiple RCT and meta-analysis, as compared with single RCT. Most studies included in our analysis are retrospective case-control studies and do not belong to the RCT category in the strict sense, which directly affects the demonstration strength of our meta-analysis result. In the future, when making systematic evaluation on multi-center RCT studies among elderly people, we are hopeful to obtain conclusive evidence on the relationship in cognitive function between homocysteine and AD, then offering directions to clinical practice and making clinical intervention strategy more rational.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Yuan Zhong, Department of Geriatrics, Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, 600 Yishan Road, Shanghai 200233, China. Tel: +8602124056053; E-mail: zhongyuan60@gmail.com

## References

[1] Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of

alzheimer's disease. Alzheimers Dement 2007; 3: 186-91.
[2] Ozkan Y, Ozkan E, Simsek B. Plasma total homocysteine and cysteine levels as cardiovascular risk factors in coronary heart disease. Int J Cardiol 2002; 82: 269-77.
[3] Williams C, Kingwell BA, Burke K, McPherson J, Dart AM. Folic acid supplementation for 3 wk reduces pulse pressure and large artery stiffness independent of MTHFR genotype. Am J Clin Nutr 2005; 82:26-31.
[4] Khandanpour N, Armon MP, Jennings B, Finglas PM, Willis G, Clark A, Meyer FJ. Randomized clinical trial of folate supplementation in patients with peripheral arterial disease. Br J Surg 2009; 96: 990-8.
[5] Brustolin S, Giugliani R, Félix TM. Genetics of homocysteine metabolism and associated disorders. Braz J Med Biol Res 2010; 43: 1-7.
[6] Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002; 346: 476-83.
[7] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560.
[8] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
[9] Cochran WG. The combination of estimates from different experiments. Biometrics 1954; 10: 101-129.
[10] Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 1998; 55: 1449-55.
[11] Folin M, Baiguera S, Gallucci M, Conconi MT, Di Liddo R, Zanardo A, Parnigotto PP. A cross-sectional study of homocysteine-, NO-levels, and CT-findings in Alzheimer dementia, vascular dementia and controls. Biogerontology 2005; 6: 255-60.
[12] Hogervorst E, Ribeiro HM, Molyneux A, Budge M, Smith AD. Plasma homocysteine levels, cerebrovascular risk factors, and cerebral white matter changes (leukoaraiosis) in patients with Alzheimer disease. Arch Neurol 2002; 59: 787-93.
[13] Miller JW, Green R, Mungas DM, Reed BR, Jagust WJ. Homocysteine, vitamin B6, and vascular disease in AD patients. Neurology 2002; 58: 1471-5.
[14] Quadri P, Fragiacomo C, Pezzati R, Zanda E, Tettamanti M, Lucca U. Homocysteine and B vitamins in mild cognitive impairment and dementia. Clin Chem Lab Med 2005; 43: 1096-100.
[15] Bottiglieri T, Parnetti L, Arning E, Ortiz T, Amici S, Lanari A, Gallai V. Plasma total homocysteine levels and the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene: a study in an Italian population with dementia. Mech Ageing Dev 2001; 122: 2013-23.
[16] Köseoglu E, Karaman Y. Relations between homocysteine, folate and vitamin B12 in vascular dementia and in Alzheimer disease. Clin Biochem 2007; 40: 859-63.
[17] Storey SG, Suryadevara V, Aronow WS, Ahn C. Association of plasma homocysteine in elderly persons with atherosclerotic vascular disease and dementia, atherosclerotic vascular disease without dementia, dementia without atherosclerotic vascular disease, and no dementia or atherosclerotic vascular disease. J Gerontol A Biol Sci Med Sci 2003; 58: M1135-6.
[18] Matté C, Scherer EB, Stefanello FM, Barschak AG, Vargas CR, Netto CA, Wyse AT. Concurrent folate treatment prevents Na+, K+-ATPase activity inhibition and memory impairments caused by chronic hyperhomocysteinemia during rat development. Int J Dev Neurosci 2007; 25: 545-52.