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**Original Research Article**

# Yizhi decoction as a therapy for vascular dementia: A meta-analysis

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## Abstract

***Purpose:*** *Vascular dementia (VD) constitutes a heavy burden in health care systems in ageing societies. This review was aimed at assessing the effectiveness of Yizhi decoction against VD.*
***Methods:*** *Five computerized databases were searched. A total of 262 publications were retrieved. Jadad evaluation was used to analyze the quality of the literature. Random methods, random allocation concealment and blinding, withdrawal, exiting and other aspects were included. RevMan 5.3 was used for meta-analysis.*
***Results:*** *There were 1045 patients, consisting of 527 cases in the treatment group (Yizhi decoction group) and 518 cases in the control group. Risk ratio revealed that Yizhi decoction was significantly effective against VD, while the weighted by mean difference demonstrated that Yizhi decoction improved the MMSE score of patients.*
***Conclusion:*** *Yizhi decoction improves the quality of daily life and mental state in VD patients. However, more rigorous and scientific case studies are still needed for further confirmation to strengthen and support these findings.*

***Keywords:*** *Vascular dementia, Yizhi decoction, Meta-analysis*


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## INTRODUCTION

The prevalence of dementia has dramatically increased in ageing populations, affecting 1 % of 60 – 64 year olds, and up to 40 % of those aged over 85 years [1]. According to the statistics from the World Health Organization (WHO), the incidence of dementia is increasing year by year. It was estimated that there were 35.6 million people with dementia worldwide in 2012, which may double in 2030 and more than triple in 2050. The Chinese population is rapidly aging. The sixth national population census showed that there were 178 million people aged over 60 years in China, accounting for 13.26 % of the total population [1]. Therefore, dementia is becoming a challenge for patients, caregivers, and healthcare providers. Moreover, it brings a heavy financial burden, because the annual care cost ranges from $17,000 to $55,200 per patient.

Three types of dementias have been identified. These are Alzheimer's disease, vascular dementia and mixed dementia. [2] As the second most common form of dementia in the elderly, vascular dementia (VD) constitutes a heavy

burden to the health care systems in ageing societies [1]. VD is a degenerative disease caused by different vascular lesions, which restricts blood supply to individual brain regions [3]. It is usually associated with cognitive dysfunctions, as well as the impairments of memory and executive function [4]. Persistent reduction in cerebral blood flow induces hypoxia/ischemia of the brain tissue, and oxygen and nutrient deprivation contribute to cell death [5]. Alzheimer's dementia (AD) and VD appear to have similar clinical symptoms, such as attention deficits and action deficits. [6]. Moreover, specific cognitive domains are affected. However, it has been reported that there were significant variations among these subtypes. AD is associated with better preserved initiative and performance than VD, according to the Interview for Deteriorations in Daily Living Activities in Dementia [2]. There are numerous studies focused on AD treatment, while VD has so far received very little attention.

Traditional vascular risk factors for VD are diabetes, hypercholesterolemia, hypertension and smoking. The association between cholesterol and small vessel disease (SVD), stroke, cognitive impairment and subsequent dementia is complicated and not yet fully elucidated. Moreover, the effect of lipids and lipid-lowering agents on the prevention or treatment of dementia is not fully understood. Studies on the effect of lipid-lowering therapy on the prevention (two trials) and treatment (four trials) of dementia found no evidence to support the use of lipid-lowering therapy [7].

Indeed, it was found that the lipid-lowering therapy was suitable for treating patients with vascular risk factors. It meet the criteria for lipid-lowering therapy aimed at primary and secondary prevention of cardiovascular and cerebrovascular events, and it was recommended for managing patients in a holistic manner based on the vascular risk profiles [7]. Various drugs, including donepezil, galantamine, and memantine, approved for the treatment of AD, have shown modest cognitive benefits on VD patients. However, their functions and benefits were inconsistent. Donepezil showed some cognitive benefits in patients with VD only, while galantamine exhibited some advantages in mixed dementia (AD and VD).

The benefits of other drugs such as rivastigmine, memantine, nimodipine, and piracetam, were uncertain. Some other supplements and herbal therapies such as citicoline, actovegin, huperzine A and vinpocetine have also been used on VD patients, but their beneficial effects were not well established. Non-drug therapies and lifestyle modifications such as diet, exercise and vascular risk factor control are important in the management of VD and should not be overlooked [8]. Acupuncture therapy stimulating the lesion area at the scalp effects. Although this treatment modality has been performed over 1000 years, it has advanced in recent years [9]. Moreover, in 1991 the WHO published the Standard International Acupuncture Nomenclature [10]. The effectiveness of scalp acupuncture for VD has been confirmed by a great deal of clinical trials [11-13].

Although the paucity of randomized control evidence is a challenge to clinical decision making, it provides multiple opportunities for on-going and future researches. The treatment for dementia using traditional Chinese medicine (TCM) has a long history, and has proved effective and safe. Yizhi decoction has produced good effects in the treatment of VD. It contains Acorus calamus, Astragalus membranaceus and Polygala tenuifolia which had higher frequency of application in the treatment of VD. In order to evaluate the effectiveness of treatment of VD with Yizhi decoction, meta-analyses were carried out on related studies from 1995 to 2016.

**Data sources**

“Vascular dementia” and “Yizhi decoction” were chosen as the key terms used to retrieve information from several databases, including Chinese biomedical literature database, China master theses full-text database, China Journal Full-text Database, VIP database, and Chinese journals of TCM database. . A total of 262 publications were retrieved. After the exclusion of repeated literature and animal experiments, 57 papers were obtained for further screening.

**Establishment of inclusion and exclusion criteria**

The inclusion criteria of clinical randomized controlled trials for Yizhi decoction in the treatment of VD were based on the International Handbook of evidence-based medicine (Cochrane) collaboration network. Alzheimer's disease patients, severe dementia patients, pseudo depressive dementia or severe depression cases, and patients with senile psychosis, schizophrenia, epilepsy and Parkinson disease were excluded. In addition, patients with heart, lung, liver and kidney diseases; hypertension, diabetes and other diseases were excluded. . The diagnostic criteria of chemical medicine consisted of two parts, one was the Chinese expert consensus on the

prevention and treatment of cognitive dysfunction, and the other one was based on the Diagnostic and Statistical Manual Spirit (4th edition), and the standard of the United States and the National Institute for Neurological Disorders and Stroke/Association Internationale pour la Recherche.

The diagnostic criteria of traditional Chinese medicine also contained two parts. One part, was the standard of diagnosis and the effective evaluation for VD reported by Tian Jinzhou [14]. The second one was the Chinese medicine treatment of dementia clinical research guideline for diagnosis mentioned in the second series of Guidelines of New Drug Clinical Medicine [15]. Randomized controlled trial (RCT) was used in the reported trials. A parallel control group was given placebo, no treatment or any other Western medicine. The balance between the groups was good and comparable. The treatment group was provided with Chinese medicine decoction. Finally, 18 articles did not accord with the diagnostic standard, 3 papers were not based on Yizhi Chinese herbal medicine, 7 were without RCT test, while 7 articles had Jadad score below 2 points. After further screening, 14 articles were found suitable for use in the study.

### Diagnostic criteria of effectiveness

Total effectiveness, simple mental state rapid test table (MMSE), difference before and after treatment, and ability of daily living ability correction scale (ADL), before and after the treatment, were used for meta-analysis and effects assessment.

## METHODS

### Evaluation standard

Jadad evaluation was used to determine literature quality, including random methods, random allocation concealment and blinding, withdrawal, exiting and other aspects. It was appropriate at 2 points, not clear at 1 point, and not appropriate at 0 point. High-quality literature was scored 3 points or higher, while low-quality literature was scored less than 3 points. Literatures with whose Jadad score less than 2 points were excluded.

### Quality assessment

Rev man 5.3 provided by the Cochrne collaboration network was used for meta-analysis. Heterogeneity test between experimental results was processed first, and the test level was $p = 0.05$. Random effects model and the fixed effects model were used when the test results appeared heterogeneous. Funnel-Plot analysis was used for analyzing in the potential publication bias. Weighted by mean difference (WMD) was used as the index of measurement for continuous variables, while odds ratio (OR) was used for classified variables. The confidence interval (CI) used was 95 %.

## RESULTS

### Literature screening

A total of 262 publications were retrieved from 5 Chinese databases, and 57 papers were selected after repeated literature and animal experiments were excluded.

**Table 1:** Jadad score of the literature

| No. | Literature | Generation of random sequences | Randomization concealment | Blind method | Withdrawal and withdrawal | Baseline equalization | Jadadd score |
|---|---|---|---|---|---|---|---|
| 1 | Liu and Li, 2014 [16] | visiting order | - | - | - | comparable | 2 |
| 2 | Li *et al* 2013 [17] | admission time | - | - | - | comparable | 2 |
| 3 | Li *et al* 2013 [18] | admission time | - | - | - | comparable | 2 |
| 4 | Li and Wang 2016 [19] | Stochastic | - | - | - | comparable | 2 |
| 5 | Gao and Liu 2015 [20] | visiting order | pharmacy | - | - | comparable | 4 |
| 6 | Sun *et al* 2015 [21] | Stochastic | pharmacy | - | - | comparable | 3 |
| 7 | Zhan *et al* 2016 [22] | Stochastic | pharmacy | - | - | comparable | 4 |
| 8 | Li *et al* 2013 [23] | admission time | - | - | - | comparable | 2 |
| 9 | Huang 2007 [24] | Stochastic | - | - | - | comparable | 2 |
| 10 | Qin and Wei 2007 [25] | visiting order | - | - | - | comparable | 2 |
| 11 | Wang 2011 [26] | Stochastic | pharmacy | - | - | comparable | 3 |
| 12 | Zhao *et al* 2015 [27] | Stochastic | - | - | + | comparable | 5 |
| 13 | Miao 2006 [28] | Stochastic | pharmacy | - | - | comparable | 3 |
| 14 | Qu 2013 [29] | Stochastic | - | - | - | comparable | 2 |

**Table 2:** Basic statistics of literature outcome indicators

| No. | Literature | N | Treatment | Control | Effect | MMSE | ADL | HDS | WMS | Bless-Roth behavior scale | Serological/ hemodynamic indices | SDSDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Liu and Li, 2014 [16] | 78 | 39 | 39 | + | + | + | | | + | | + |
| 2 | Li *et al* 2013 [17] | 48 | 24 | 24 | + | + | + | | + | | + | |
| 3 | Li *et al* 2013 [18] | 46 | 23 | 23 | + | + | + | | | | + | |
| 4 | Li and Wang 2016 [19] | 40 | 20 | 20 | + | + | + | | | | | |
| 5 | Gao and Liu 2015 [20] | 60 | 30 | 30 | | + | + | | | | | + |
| 6 | Sun *et al* 2015 [21] | 86 | 43 | 43 | + | + | + | + | + | | + | |
| 7 | Zhan *et al* 2016 [22] | 115 | 58 | 57 | + | + | + | + | | | | |
| 8 | Li *et al* 2013 [23] | 70 | 35 | 35 | + | + | + | | | | + | |
| 9 | Huang 2007 [24] | 76 | 38 | 38 | + | + | + | | | | | |
| 10 | Qin and Wei 2007 [25] | 61 | 33 | 28 | + | + | + | + | | | | |
| 11 | Wang 2011 [26] | 83 | 42 | 41 | + | | | | | | | |
| 12 | Zhao *et al* 2015 [27] | 102 | 52 | 50 | | + | + | | | | + | + |
| 13 | Miao 2006 [28] | 60 | 30 | 30 | | + | | | | | | |
| 14 | Qu 2013 [29] | 120 | 60 | 60 | + | | | | | | + | |

Through inclusion and exclusion criteria, 14 RCT were finally chosen, including 6 high quality RCT articles and 8 low-quality RCT articles. Total efficiency was recorded in 11 articles, curative effect of TCM syndrome was reported in 3 articles, MMSE score was reported in 12 articles, and ADL was mentioned in 11 articles. Moreover, Kyohko Hasegawa Dementia Scale was used in 3 articles, WMS score was recorded in 2 articles, while blood flow index was mentioned in 6 articles. There was a total of 1045 patients, including 527 cases treated with *Yizhi* decoction group, and 518 cases in the control group. These details are shown in Table 2.

## Determination of publication bias

Funnel plots produced using Revman 5.3 analysis software were used to detect publication bias. Results showed absence of publication bias. Therefore, the conclusions were reliable.

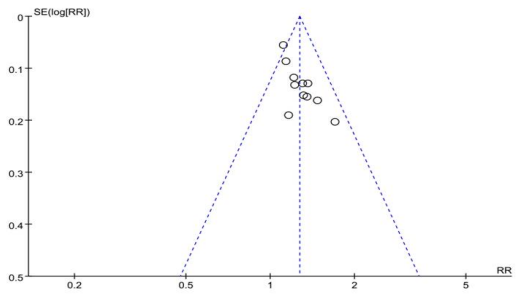


**Figure 1:** Funnel diagram of general therapeutic effect of *Yizhi* decoction on VD

## Results of meta-analysis of total effectiveness

A total of 14 papers were screened, and 11 of them reported the total effectiveness of *Yizhi* decoction in the treatment of VD. Meta-analysis was carried out on 11 observational data, and the results are shown in Figure 2. The total effectiveness for the studies showed homogeneity (heterogeneity test = 10.88, $p$ =0.37). Thus, the Risk Ratio (RR) of the combined effect was analyzed usingthe fixed effect model. The RR merger was 1.27, and the 95% confidence interval was between 1.18 and 1.37, indicating that the RR value was statistically significant, which suggest that *Yizhi* decoction was effective in the treatment of VD.

## Meta-analysis results for MMSE

A total of 12 studies measured MMSE before and after treatment, and 11 descriptive methods were used to describe the differences among MMSE scores before and after treatment. These 11 articles were used to study the change of MMSE score after the treatment with weighted mean difference. The results (Figure 4) indicated that the 11 items had heterogeneity (heterogeneity test = 19.93, $p$ = 0.03). Therefore, the combined effect of the WMD was analyzed using a fixed effects model. The WMD was 3.6, and the 95 % CI was between 3.14 and 4.07, which indicated that the WMD value was statistically significant.

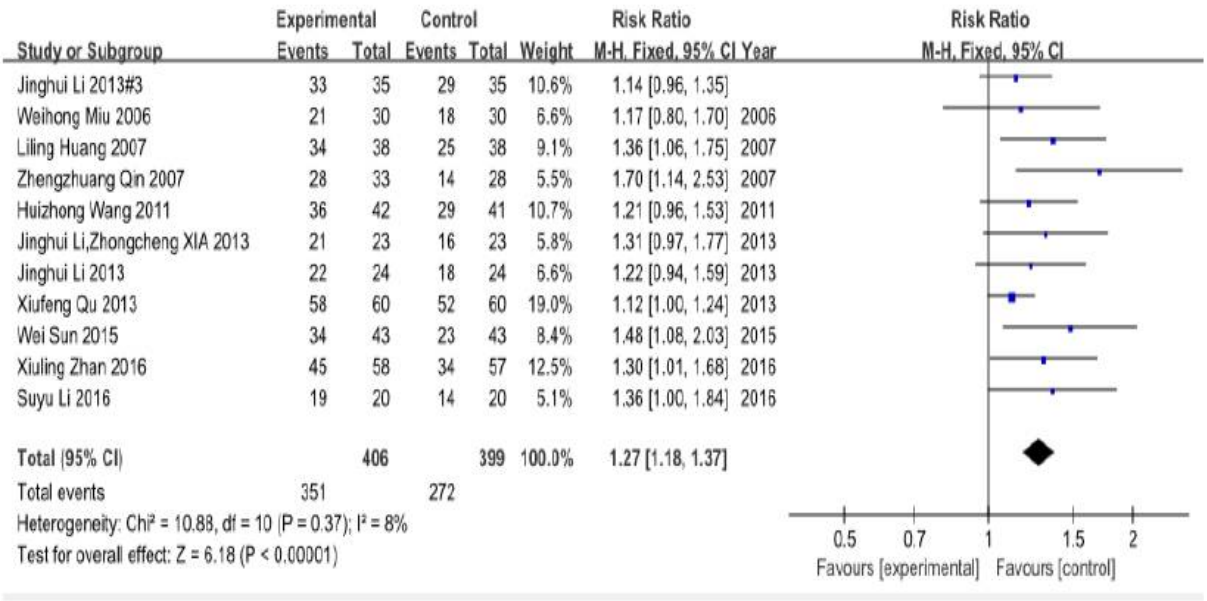


**Figure 2:** Forest diagram of the therapeutic effect of *Yizhi* decoction on VD

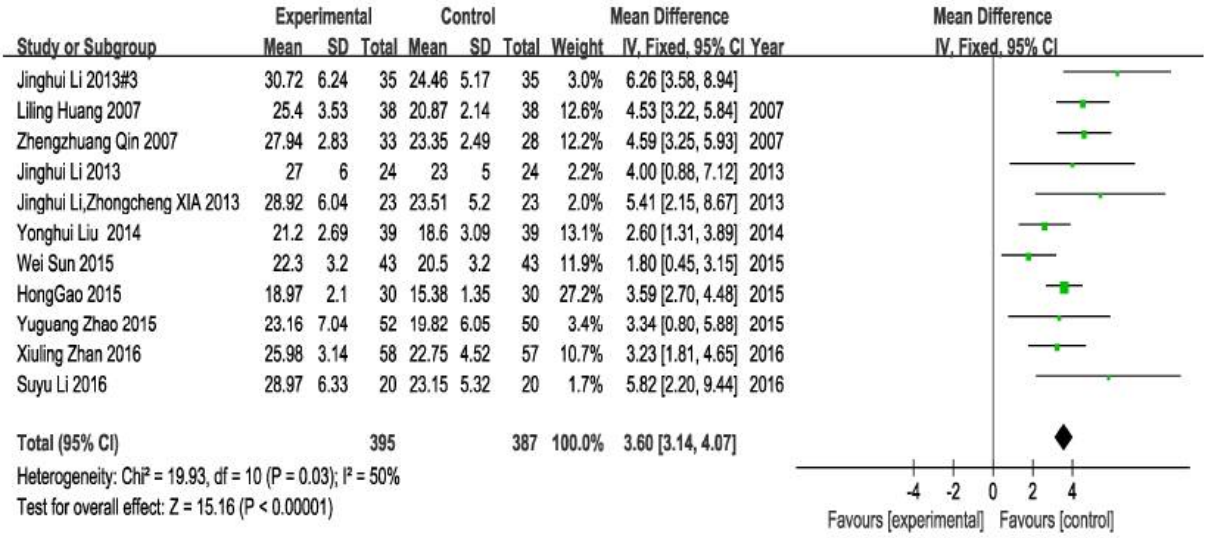


**Figure 3:** Forest chart of simple mental state quick check list

Thus, it was inferred that *Yizhi* decoction improved the MMSE score of patients with VD.

**Meta-analysis of ADL scores**

ADL scores before and after treatment were reported in 11 studies, and 10 studies which referred to the differences were analyzed. The 10 studies were with homogeneity (heterogeneity test = 46, $p < 0.00001$). Therefore, the analysis of the combined effect of IR used a random effects model. The IR was 1.44, its 95 % confidence interval was between 5.72 and 2.84, which indicated that the IR value was statistically significant. Sensitivity analysis (Figure 3) indicated that the result was stable and reliable.

**Subgroup analysis**

***Based on time of administration***

Subgroup analysis included two groups: within 30-days group (including the 30 days, regarded as short-term medication group) and more than 30-days group (regarded as long-term medication group). The analysis was conducted based on the MMSE scores. There were 5 articles for short-term medication, and 9 articles for long-term medication. The MMSE scores were reported in 6 articles of long-term medication, and $I^2$ (index of heterogeneity) was 97 % > 50 %. This indicated that the analyzed subjects were heterogeneous. Therefore, the random effects model was used to analyze.

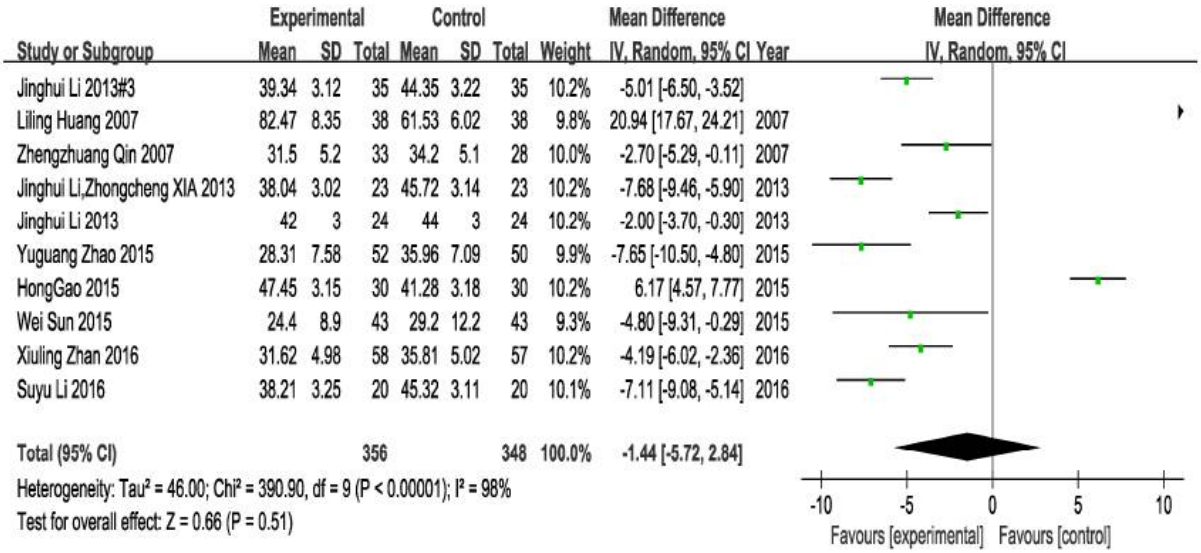


**Figure 4:** Forest map of correction scale score of daily life ability

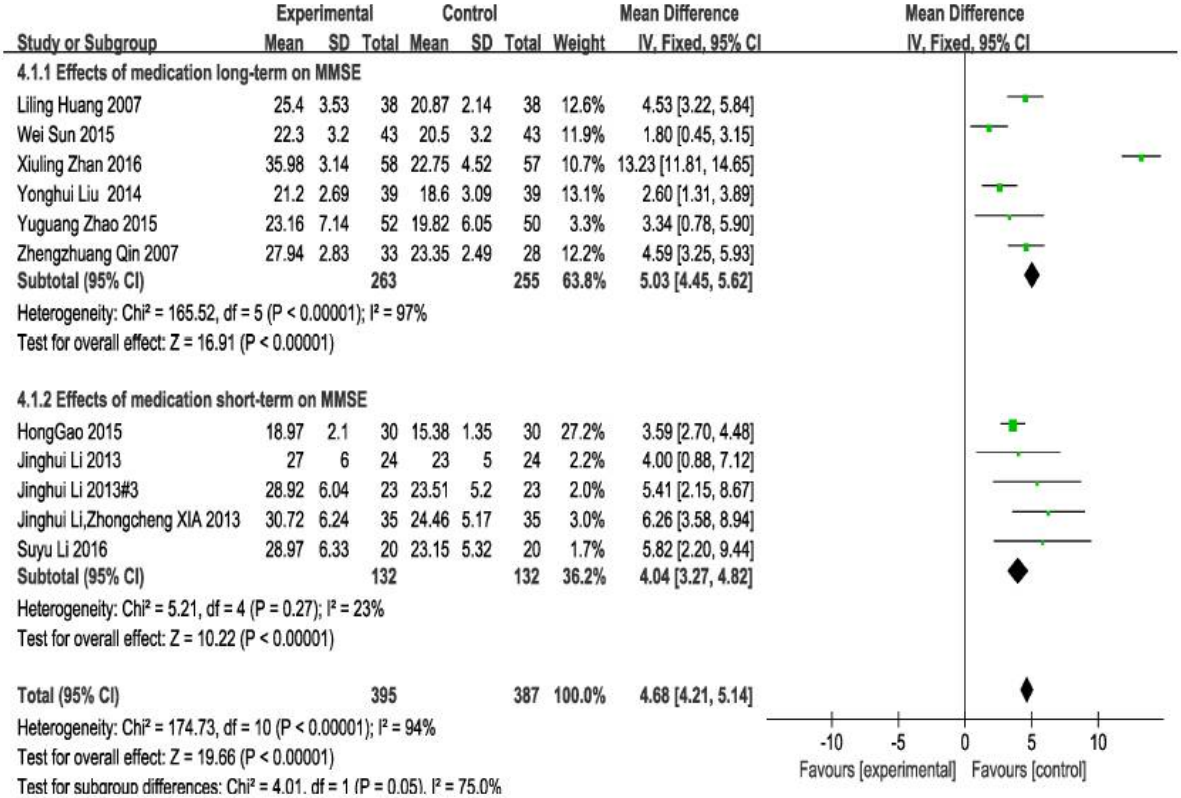


**Figure 5:** Forest map of subgroup analysis for MMSE score of time

Merged MD value amounted 5.03, the 95% confidence interval was between 4.45 and 5.62, and the overall effect test Z was 16.91, $p < 0.05$. There were 5 articles on short-term medication reported MMSE scores, and $I^2$ was 23 % < 50 %, which meant that the 5 subjects were with homogeneity. Thus, the fixed effect model was used. The rhombus was at the right of the vertical; merged MD value was 4.04, and the 95 % confidence interval was between 3.27 and 4.82. The overall effect test Z was 10.22, ($p < 0.05$) and the result of MMSE score is shown in Figure 5.

The subgroup analysis was used for two ADL key evaluation indices, and groups were divided by MMSE scores. There were 5 articles for long-term medication, and the $I^2$ (index of heterogeneity) was 98 % > 50 %, which indicated the analyzed subjects were heterogeneous. Therefore, the random effects model was used

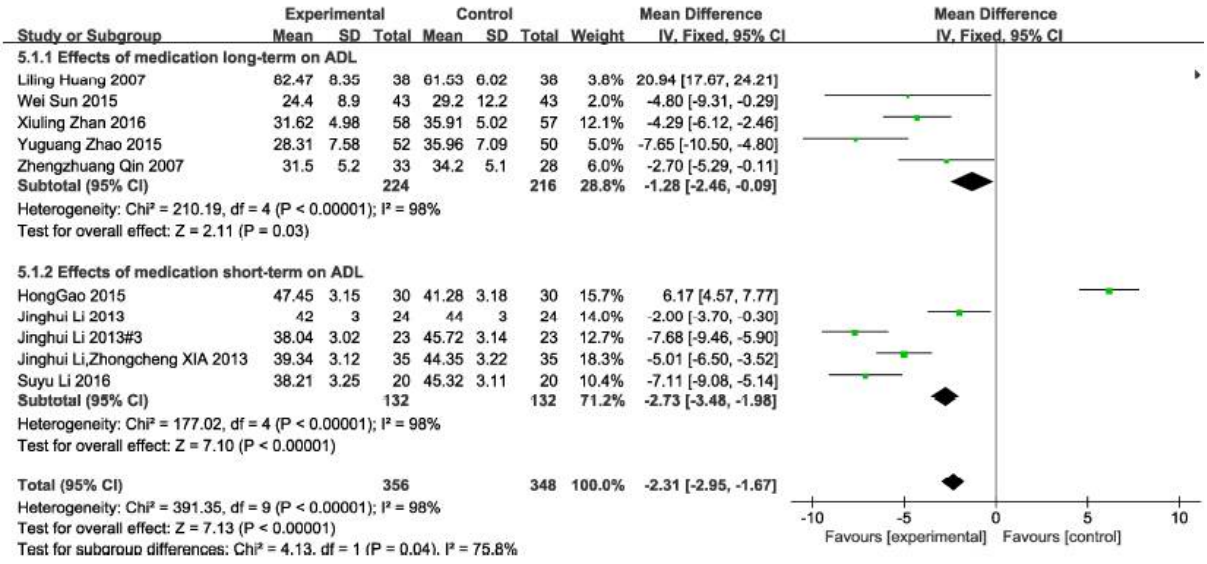


**Figure 5:** Forest map of subgroup analysis for ADL score of time

for analysis. Merged MD value was -1.28, with 95% confidence interval between -2.46 and -0.09, and the overall effect test Z was 2.11 ($p < 0.05$). There were 5 articles on short-term medication that reported ADL scores. The $I^2$ was 98 % > 50 %, which meant that the 5 subjects were heterogeneous. Thus, the random effects model was used. The rhombus was at the left of the vertical, and merged MD value was -2.73; the 95 % confidence interval was between -3.48 and -1.98, and the overall effect test Z was 7.1 ($p < 0.05$). The result of analysis of ADL scores is shown in Figure 5.

***Based on intervention method***

Groups were divided into those administered *Yizhi* alone and those administered *Yizhi* in combination. The analysis was conducted based on the MMSE scores. It could be seen that 7 articles on *Yizhi* administered alone reported MMSE scores, and $I^2$ was 55 % > 50 %, which showed that the analyzed subjects were with heterogeneity. Thus, the random effects model was used for analysis. Merged MD value amounted to 3.44, with 95 % confidence interval between 2.83 and 4.05, and the overall effect test Z was 11.09 ($p < 0.05$). There were 4 articles on *Yizhi* administered in combination, and they reported MMSE scores. The $I^2$ was 50 %, which implied that the subjects included in the study had homogeneity, and the fixed effect model was used for analysis. The rhombus was at the right of the vertical, merged MD value was 3.84, the 95 % confidence interval was between 3.11 and 4.56, and the overall effect test Z was 10.37 ($p < 0.05$). The results are shown in Figure 6.

The subgroup analysis was for two ADL key evaluation indices, and groups were divided based on MMSE scores. It could be seen that there were 7 articles on the *Yizhi* administered alone that reported ADL scores, and $I^2$ was 97%>50%. It indicated that the analysis object had heterogeneity, so the random effects models was for analysis. Merged MD value was -2.98, with 95 % confidence interval between -3.67 and -2.30, and the overall effect test Z was 8.5 ( $p < 0.05$). There were 3 articles on *Yizhi* administered in combination, with ADL scores, and the $I^2$ was 99 %, meaning that the subjects included in the studies had heterogeneity. Thus, the fixed effect model was used. Merged MD value was 1.75; the 95 % confidence interval was between 0.09 and 3.14, and the overall effect test Z was 2.06 ($p < 0.05$). These results are shown in Figure 7.

## DISCUSSION

This study has shown that *Yizhi* decoction improved the quality of daily life and mental state of VD patients, on the basis of the results from clinical total effectiveness, and the ADL and MMSE meta-analysis. There are several limitations in this study. Firstly, a few foreign data were we disregarded. This might be one of the reasons for publication bias in the meta-analyses. Secondly, due to limited or missing data on subsets in the current trials, there are still several details missing. It was not possible to assess the long-term curative effect and the influence on the life quality and the mortality for VD patients on *Yizhi* decoction therapy. Because all the studies did not report the quality of living of the patients, follow-up and mortality of patients after treatment are not known. The evaluation

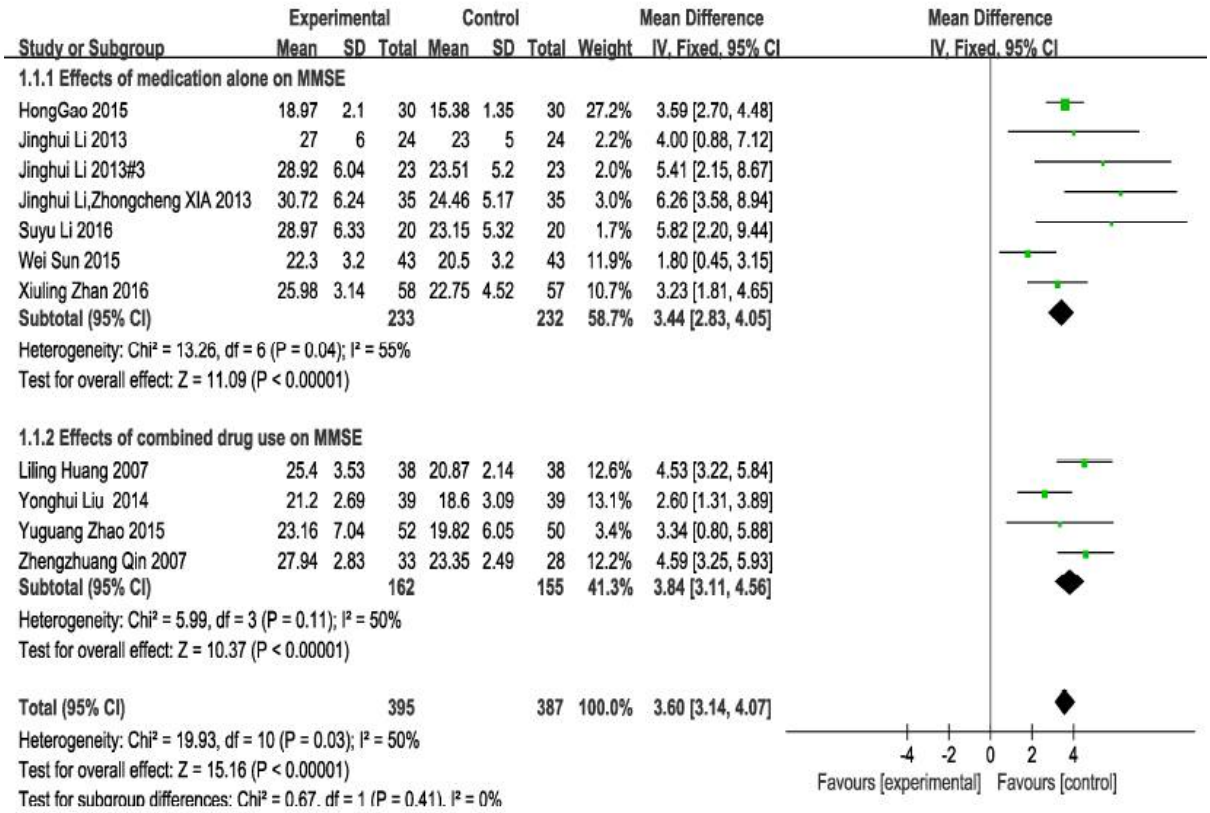


**Figure 6:** Forest map of subgroup analysis for MMSE score of intervention method

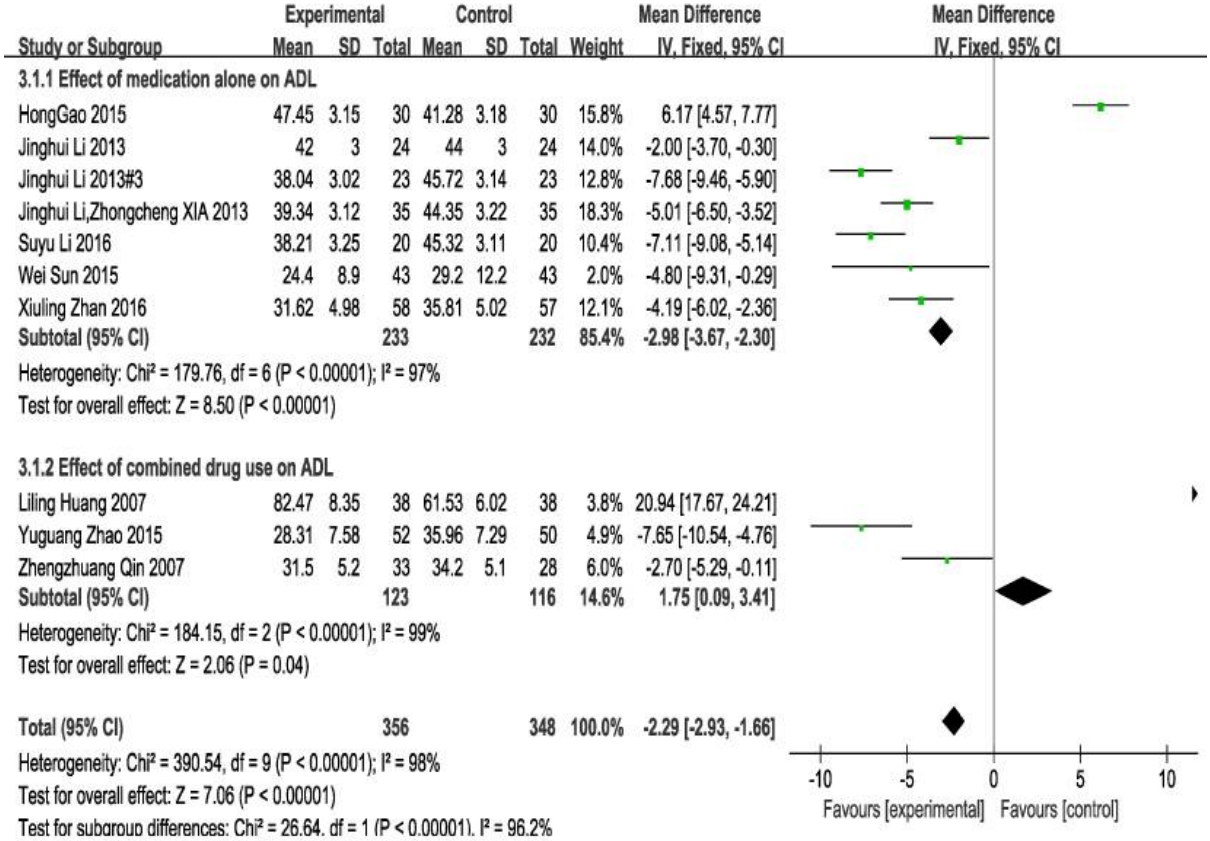


**Figure 7:** Forest map of subgroup analysis for ADL score of intervention method

system was low quality, the literature description of randomization was not clear enough, and most randomized allocation schemes were not hidden. Moreover, most of the literature were not blinded, and there were midway withdrawals. These factors limited the credibility and effectiveness in the treatment group. The literature had different treatment methods for the control group, and the sample included in articles was small. Therefore, larger sample studies with more rigorous scientific evaluations are needed for further confirmation.

## CONCLUSION

*Yizhi* decoction improves the quality of daily life and mental state in VD patients. However, more rigorous and scientific case studies are still needed for further confirmation to strengthen and support these findings.

## DECLARATIONS

### *Acknowledgement*

The authors thank the reviewers for their critical comments on the manuscript.

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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