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Effectiveness of Acupuncture Treatment on Dementia with Declined Cognition: Systematic Review and Meta-analysis

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JAE WON BAE

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APPROVED BY RESEARCH COMMITTEE

Shanqin Cui, OMD, L.Ac, Professor

Soo Gyung. Kim, OMD, L.Ac, Doctoral Program Director, Professor

Ki Haeng Cho, Ph. D, L.Ac, Program Director, Professor

Seong Hwa Hue, DAOM, L.Ac, Doctoral Clerkship Coordinator

Joseph H. Suh, Ph.D, OMD, L.Ac, Doctoral Research Coordinator, Professor

South Baylo University

Anaheim, California

June 13, 2019

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JAE WON BAE

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Research Advisor: Dr. Qiwei Zheng

ABSTRACT

Acupuncture has positive effects on the treatment of the dementia through clinical observation and experts' recommendations. However, its potential benefits for the treatment on dementia are ambiguous and still require systematic evaluations. Therefore, a systematic review and meta-analysis was performed to estimate the overall efficacy and effectiveness of acupuncture for the treatment on dementia. Related trials were searched through August 2018 from three databases: Cochrane Library, PUBMED, and EBSCO host. The Cochrane Risk of Bias Tool was used for the assessment of methodological quality. Review Manager v.5.3 software was applied to achieve a meta-analysis of comparative effects, and Egger's test was fulfilled in order to examine publication bias. Although heterogeneity among 12 outcomes for four studies was high as many as I^2 = 74%, a total effect of acupuncture therapy on dementia provided statistical significance; SDM [95% *CI*]: 0.37 [0.14, 0.60], p = 0.002, I^2 = 74%. 11 outcomes but MMSE with three studies were evaluated with one study. Four outcomes showed significant results; ADAS-cog (1.01 [0.56, 1.45], p < 0.0001), NPI (1.13 [0.67, 1.58], p < 0.00001), Picture recognition (0.61 [0.29, 0.93]), and Living ability (0.78 [0.27, 1.29]) respectively. But eight outcomes were not statistically significant; ADCS-ADL (-0.07 [-0.49, 0.35], p = 0.75), MMSE (0.32 [-0.22, 0.87], p = 0.72, I2 = 76%), ADL (0.11 [-0.48, 0.70], p =

0.72), DEMQOL (0.52 [-0.08, 1.I^2]), Clock drawing (-0.05 [-0.37, 0.26], BBS (0.19 [-0.30, 0.67]), Directional ability (-0.01 [-0.50, 0.45]), Short-term memory (-0.03 [-0.52, 0.45]). From those results, it was concluded that acupuncture treatments are helpful to improve the cognition, memory, living ability, and learning in cognitively uninjured or injured older adults.

Abbreviation: MMSE= Mini Mental Status Examination, ADAS-cog =Alzheimer's disease Assessment Scale-Cognitive, NPI=Neuropsychiatric Index, ADCS-ADL=Alzheimer's disease Cooperative Study-Activities of Daily Living Scales, ADL =Activities of Daily Living Scale, DEMQOL= Dementia Quality of life questionnaire, BBS=Bless Behavior Scale, RCT = randomized controlled trial, *SMD* = standardized mean difference, *CI* = confidence interval, and I^2 =Higgin's statistics

Key words: dementia, cognition, memory, acupuncture, systematic review, meta-analysis, and RCT.

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I. INTRODUCTION

Dementia is the failure of mental ability that affects normal activities of daily living, continuing in excess of six months, not involving with a loss or change of consciousness as well as not existing since birth. According to US Department of Health and Human Services, [1] Dementia is the fourth leading cause of death in the United States and the precise popularity is unidentified. However, there are around four million Americans with dementia and another three million suffer from mild cognitive impairment. [1], [2]

The loss of cognitive abilities as one of symptoms in dementia due to gradual death of brain cells causes deteriorations in memory, reasoning, planning, and personality. Although the dementia is more common in elderly, it is not an inexorable portion of aging but the specific brain disease. It is the most common cause that Alzheimer's disease (AD) is followed by vascular or multi-infarct dementia. It is hard to determine the occurrence of dementia because there are disparities of definition among different studies and some normal waning in functional ability with age. Dementia involves 5–8% of all people from 65 years old to 74 years, and up to 20% of those from 75 years old to 84 years. Approximations for dementia in those 85 and over vary from 30–47%. There are roughly about two to four million Americans with Alzheimer Dementia. The number of people with Dementia is anticipated to increase more than 14 million by half of the twenty-first century to the population as a whole age. The cost of dementia lead to huge amount of expense because most people with dementia do not have income losses from their disease, already having been retired. Therefore, the cost of care increases financial burdens in our society such as lost wages for family caregivers, medical supplies and drugs, home alterations for the safety, and the increasing cost of nursing home care. In addition, there is the

psychological cost easily not calculated. For examples, losing control of many requisite performs in their life and personality, a burdens of family member from dependence and unpredictability of people with dementia. [3]

Generally, Dementia results from the cerebral cortical degeneration of the brain that controls thinking, memory, and personality lead mainly to dementia. A cognitive disorder that is characteristic of dementia is caused by the death of cells in the cerebral cortex. Alzheimer disease is composed of half to three quarters among all cases and the main common cause in dementia. There are two abnormal structures, named senile plagues and neurofibrillary tangles, overfilled in the brain of the person with AD. Senile plaques are comprised of the beta amyloid deposits between neurons and neurofibrillary tangles are twirled bulks of protein fibers in neurons. It is not clear the reason why these abnormal structures develop. [6] According to recent researches [4,5], it is said that inflammation, blood flow restraint, and free radicals such as toxic molecules lead to abnormal structure in brain cells. Also, several genes, having its exact role uncleared, have been related higher rates of AD.

Vascular dementia accounts for 5- 30% of all dementia and results from lack of blood flow into the brain caused by a sequence of small strokes, known as multi-infarct dementia. Other cerebrovascular causes include Vasculitis from syphilis, Lyme disease, or systemic lupus erythematosus, subdural hematoma, and subarachnoid hemorrhage. The cause of vascular dementia is the sudden onset of symptoms, which occurs more rapidly than Alzheimer's disease. With the emergence of new stroke, symptoms may be proceeded. Compared to AD, the prevalence of vascular dementia decreases after age 75. [3]

Additionally, there are other conditions, causing dementia: brain tumor, Parkinson′s disease, Hunting′s disease, Lewy body disease, Creutzfeldt-Jakob disease, multiple sclerosis, Pick′s

disease, AIDS, hydrocephalus, hypothyroidism, abuse of alcohol or other drugs, head trauma, vitamin deficiency (thiamin, niacin, or B12), hypercalcemia.

Dementia is manifested with a steady diminishment of thinking and other mental activities and ultimately have an effect on every side of mental life. In contrast to delirium, slow progressive dementia has symptoms such as delirium, but with a very rapid onset and fluctuation process with changes in consciousness levels. However, delirium may emerge with dementia, especially because people with dementia are more vulnerable to many types of drugs that can cause delirium.

There are many symptoms in the person with dementia such as: the loss of memory, diminished thought and planning, linguistic and understanding disorders, lack of judgment, poor orientation, reduced attention and soared restlessness (disorientation and memory losses result in wandering leading to significant safety issues), personality problems and mental illness.

Dementia makes progress slowly, making it difficult to diagnosis it early. It may be required that people suspected of dementia visit the clinic frequently or for several months to find the correct diagnosis. Diagnosis starts with a comprehensive physical exam and full medical history as well as mentions from caregivers and family members. A family history such as AD and cerebrovascular disease may present clues to the cause of symptoms. In order to find alterations in the person′s cognitive ability, simple tests of mental function such as MMSE (Mini Mental State Examination) [14,15] and HDS [16] are used with word recall, object naming, and number-symbol matching. Depression in the elderly can be misdiagnosed as dementia so it is important to rule out depression from the Hasegawa′s Dementia Scale diagnosis of dementia. It is also critical to separate dementia from the mild normal cognitive deterioration of progressive age. [7,8] The full list of drugs in the medical history is need to find a number of drugs to induce dementia-

like symptoms. A diversity of medical tests may be required to find the cause of dementia and conform the most possible etiology. MRI scans or CT, X-rays, vascular imaging studies may be used to diagnosis tumors, cerebrovascular disease, hydrocephalus. Hormone imbalances or nutritional deficiencies may be discovered by blood tests.

If possible, the triggering disease should firstly be treated to deal with treatment of dementia. For example, the dementia can be improved, resulting from hormonal issues, malnutrition, tumor, drugs to a certain degree. Stroke-linked dementia should be treated as smoking halt, aspirin therapy, and controlling hypertension in order to reduce the risk of additional strokes. Even though vitamin E, aspirin, selegiline estrogen are recently helpful to slow the progression of AD, any therapies cannot revere the progression of AD which makes the patients become totally dependent. Education about AD or Dementia is needed as early as in the disease progression, in order for patients and their family to predict and strategy for unavoidable changes.

Medication, psychotherapy, and environmental adaptations should altogether be collaborated to deal with symptoms of dementia. Drugs [11] such as donepezil (Aricept) and tacrine (Cognex) are usually recommended for the treatment of AD. The action of transmitting substance, called acetylcholine, sending chemical signals between cells in the brain is impeded and delayed by these drugs. Approximately 40% of patients with mild to moderate AD showed a transitory change in cognitive functions. Hydergine is occasionally recommended despite of having dubious benefit for most patients.

Psychotic symptoms [8], including paranoia, delusions, and hallucinations, may be treated with antipsychotic drugs, such as haloperidol, chlorpromazine, risperidone, and clozapine. Side effects of these drugs can be significant. Antianxiety drugs such as Valium may improve behavioral symptoms, especially agitation and anxiety, although BuSpar has fewer side effects.

The anticonvulsant carbamazepine is also sometimes prescribed for agitation. Depression [9,10] is treated with antidepressants, usually beginning with selective serotonin reuptake inhibitors (SSRIs) such as Prozac or Paxil, followed by monoamine oxidase inhibitors or tricyclic antidepressants. [11,12] Electroconvulsive therapy may be appropriate for some patients with severe depression who are unresponsive to drug therapy. In general, medications should be administered very cautiously to demented patients, in the lowest possible effective doses, to minimize side effects. Supervision of taking medications is generally required.

There are several drugs being tried to decelerate the progress of AD: Acetyl-l-carnitine, Propentofylline, Milameline,[17,18] and Ginkgo[19,20] extract. Acetyl-l-carnitine works on the mitochondria (the energy cell structures), Propentofylline may assist circulation, and Milameline works like tacrine and donepezil. Ginkgo extract from the leaves of Ginkgo tree meddles with the platelet activating factor (a circulatory protein) and has been recommended to enhance oxygenation and circulation to brain for a long time in Asia and is broadly advised in Europe for helping blood circulation.

Chi dai, dementia in TCM (Traditional Chinese Medicine) or retarded mental activities and disorientation, has been clearly described and documented in numerous ancient texts. As early as in Nei Jin, [21] partial manifestations and pathogeneses were elaborated. For instance, in Ling Shu [22] Chapter 33, "Brain is sea of the marrow ... sufficient sea of the marrow ensures rigorous strength, and intact voluntary movement and coordination of the body parts ... deficient sea of the marrow causes dizziness, tinnitus, vertigo, soreness of the lower back, impaired visual acuity, weakness and loss of control to the body parts." In Ming dynasty, scholar Zhang, Jingyue first formally named this disorder chi dai. In Qing dynasty, the scholar, Chen, Shiduo, dedicated a single chapter to discuss chi dai as a distinctive disorder in his book, Bian Zheng Lu.

According to this publication, chi dai is "Initiated by liver qi stagnation and ended as stomach qi failure; constrained liver leads to wood overacting on the earth; phlegm is accumulated in the chest and lodged around the heart; spirit is misted and the mind's function is deteriorated, manifested as chi dai." However, it was the other scholar, Wang, Qingren, during the Qing Dynasty, categorized chi dai into pathology of the brain, "Poor memory in children is caused by unfilled sea of the marrow since the development and growth has not been fully matured; however, poor memory in advanced age signifies a deficiency in sea of the marrow." Conclude from the previous discussion, chi dai, or dementia, pertains to pathology of the heart and kidney; the spleen and liver also play significant roles to the pathogenesis. Deficiency of sea of the marrow results from multiple pathologies, including congenital deficiency, depletion due to chronic illness, and deterioration of the essence related to advanced age. Spleen and stomach deficiency with phlegm generation and emotional stress, induced liver constraint with qi stagnation and blood stasis, may contribute to the occurrence of chi dai by causing malnourishment of the mind or phlegm misting the clear orifices. [23]

From ancient time, Acupuncture has been considered as the chief treatment in Asia. So, the elderly are accustomed to acupuncture treatment. Acupuncture treatment refers to technique for balancing the flow of energy or life force - known as chi or qi (chee) -believed to flow through pathways (meridians) in the body. By inserting needles into specific points along these meridians, the energy flow will re-balance. Recently, many studies have been performed to evaluate the effectiveness of Acupuncture treatment and the results generally showed efficacy and safety for neurological diseases such as MCI, schizophrenia, vascular dementia, stroke, depressive symptoms, Parkinson′s disease, and Alzheimer′s disease.

However, a systematical review of studies on the effects of the acupuncture treatment on the patients with Dementia has rarely been performed to date. As such, it is expected that Oriental medicine such as Acupuncture, herbs, etc. will have many possibilities in the treatment of dementia, but it is absolutely insufficient in the quantity and quality of supporting evidence.

The purpose of this study was to investigate the effects of oriental medicine on the treatment of dementia through systematic review and meta-analysis of randomized comparative clinical trial reports on the treatment of dementia using oriental medicine from 2000 to 2019 according to PRISMA.[24] The retrieval and evaluation of data for systematic review follows the method of NECA systematic review manual and refer to Cochrane Collaboration method.

If the results of this study demonstrate that the acupuncture treatment improves cognitive function, the global clinical field and even medical policy as well as Oriental medical realm would be greatly influenced.

II. MATERIALS AND METHODS[36]

1. Retrieval Strategy and Study Selection[36]

In this study, the research papers from 2010 until 2019 were reviewed to assess the effectiveness of the acupuncture treatment of Dementia by MMSE Tool. The research papers were selected among the research topics applied by Dementia as the research topic, Acupuncture as the treatment method, and RCT (Randomized Controlled Trials) as the research method. (Table 1)

Table 1. Formation of the EBM Question Based on PICOS rule.

PICO	EBM Question Problem
Problem	Dementia
Intervention	Acupuncture
Comparison	Control
Outcome	Improvement of mental ability
Study Design	Randomized controlled trials

Relevant RCTs were systemically retrieved from the following databases: PubMed, Ovid-MEDLINE, EMBASE, and EBSCO Research Database, from their commencement to March 2018 using the search terms of “Dementia,” “acupuncture,” “randomized controlled,” by Boolean Connectors such as AND and OR.(Data base for literature retrieval was shown in Table 2.)

Table 2. Data Base for Literature Retrieval

Data Base	Indexing Thesaurus	URL
PubMed	MeSH	http://www.ncbi.nlm.nih.gov/pubmed/
Ovid-MEDLINE	MeSH	http://ovidsp.tx.ovid.com
EMBASE	EMTREE	http://www.EMBASE.com
EBSCO Research Database	MeSH	http://web.ebscohost.com

In addition, the reference lists on the involved studies were moreover inspected by hand in order not to omit the possibly entitled trials. Subsequently, the full-texts of all the entitled studies classified were reevaluated, and the data of study were extricated using a unified form.

2. Data Extraction and Converting[36]

1) Extracted Data Items

The data items included Literature Information, the reason of inclusion and exclusion, the study methods, the number of participants in experimental and control groups, interventions, outcomes, results, and others in order to extract the data for the systemic review and meta-analysis from the selected literatures. (Table 3)

Table 3. Data Items Extracted from the Selected Literature.

Data Component	Data Item
Literature Information	Literature ID
Eligibility	□ Selection or Exclusion □ Reason for Exclusion
Methods	□ Study Design □ Period of trial □ If RCT, - Order of randomization, Concealment of randomization order, Blinding, Other factors to evaluate the bias
Participants	□ Sample size, Clinical setting, Diagnostic criteria, Age, Gender, Comorbidity, socio-demographic characteristics, ethnicity, Study timing
Interventions	□ Number of intervention groups □ Method of intervention, Repeatability of intervention, Integrity of intervention
Outcomes	□ Outcome and timing of intervention, Timing of data collection, Timing of report □ Definition of outcome (including diagnostic criteria), Unit of data, Value and meaning of maximum and minimum scale data
Results	□ Sample size, Missing data, schema, Mean and standard deviation from continuous variables, Confidence intervals, p-value, Significance,
Others	□ Sponsor of research fund

2) Conversion of the data

The quantitative results of the same values were derived comparing the average value, the median, the standard deviation, the standard error, the odds ratio, the relative risk, etc. from the extracted data. The Cochrane Collaboration Review Manager 5.3(RevMan 5.3) were applied in this meta-analysis using the standardized mean difference (SMD) and 95% confidence interval

(CI) in the experimental group and the control group.

3. Assessment of Risk of Bias in Included Studies[36]

Generally, in the systematic review and meta-analysis about randomized controlled trials, the type of risk of bias occurs as Classification scheme for bias (Table1on Appendix), and Evaluation Items and Criteria for Judging Risk of Bias in the 'RoB' Assessment (Table 2 on Appendix).

The risk of bias on each selected study was evaluated according to RevMan5.3 software on the basis of the following 7 realms: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. (Bias Tables)

4. Assessment for Level of Evidence[36]

In order to evaluate the basis level of selected literature for systematic review, using the GRADE profiler software developed by Grading of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group, the following items were comprehensively assessed :1) research design, 2) risk of bias, 3) non-coherence, 4) non-directivity, 5) inaccuracy, 6) publishing bias,7) the estimate of effect 8) the effects of disturbance variables, and 9) evaluation of the Dose-Response relationship. Levels of evidence for individual outcomes were graded as shown in Table A-III of Appendix II. The overall results were not graded separately.

5. Assessment of Heterogeneity

Unless it could be explained by chance that variations in the results of individual studies

were more than sampling error, it was examined through the forest plot whether the directionality of the value overlaps with the confidence interval. If confidence intervals did not overlap and there was only a small overlap, statistical testing was performed. Statistical tests for heterogeneity testing include Q statistics and Higgin's I^2 statistics, and calculated using Review Manager 5.3

1) Q statistics (Chi square test) [25]

Q statistics show that there is the distance between the intervention effect of each study and the pooled effect across studies in values. The *p*-value was 0.10 at a statistically significant level. The formula for obtaining the *Q* value at this time is shown in Appendix I.

The null hypothesis is that there is no basis for heterogeneity. The antagonistic hypothesis is that there is a basis for heterogeneity. If *p*-value is above 0.10, the null hypothesis is adopted so Fixed-effects model in Meta-analysis is performed. If *p*-value is below 0.10, reject the null hypothesis and consider a meta-analysis of the random-effects model.

2) Higgin's I^2 statistics [25,26]

Higgin's I^2 statistics was used to quantify inconsistencies, the degree of heterogeneity was depended on the I^2 value from the following formula in Appendix I.

The criteria are as follows in order to analyze the heterogeneity.

$0\% \leq I^2 \leq 40\%$: heterogeneity may not be important

$30\% \leq I^2 \leq 60\%$: may have moderate heterogeneity

$50\% \leq I^2 \leq 90\%$: practically probable heterogeneity

$75\% \leq I^2 \leq 100\%$: significant heterogeneity

6. Meta-analysis

RevMan 5.3 was used for meta-analysis. If the p value from Q statistics is greater than 0.10, a meta-analysis of the fixed effect model is performed. If the *p*-value is less than 0.10, the meta-analysis of the variable effect model was performed.

1) Fixed-effects model

The fixed effect model presents a weighted average to a series of study estimates. The inverse of the estimates' as study weight is usually applied to the weighted average in order that larger studies predispose to influence to the weighted average compared to smaller studies. In this case, the reciprocal of the variance of the effect estimates was used for the weights, and the formula for the weights and weighted averages is shown in Appendix I.

2) Random-effects model

This model is used to synthesize heterogeneous research and simply weight the average from the effect sizes of group studies. In order to analyze the overall effect, DerSimonian-Laird's variable effect model with the unequal shape was applied

3) Calculation of effect size

For the effect size of each item calculated through the meta-analysis, Cohen's d value, which standardizes the mean difference to the standard deviation, was achieved by formulas in Appendix (15) and (19). According to the criteria of Lipsey et al., the value of d was classified into three types; less than 0.32 is for the small, 0.33 to 0.55 is for the medium, and 0.56 to 1.2 is

for the large, comparing the mean difference and p-value.

7. Assessment of Reporting Bias [36]

In order to identify reporting bias such as publication, time lag bias, multiple publications, location bias, citation, language, and outcome, the funnel plot was attained by Review Manager 5.3 for preventing the overestimation of summary estimates in the effectiveness of treatment.

8. Confirmation of Safety and Side Effects[36]

The safety and adverse effects of the intervention were identified using the rationale in the literature.

9. **Ethical Review**

This systematic review was reviewed and determined as an exempt case from evaluation by Institutional Review Board of South Baylo University on November 29th, 2018.

III. RESULTS

1. Selection of research literature

Through the electronic data search, reference review of related research, EBM search engine, the result in searching the research papers about the effectiveness of acupuncture treatment about Dementia from 2010 until 2019 was shown in Table# and Figure #.
With "Dementia" as a search term, all 13,857 documents were searched, combined with "acupuncture" using the operator "AND", 79 documents were found. Three clinical studies were obtained by reviewing the references of these papers. This result was combined with "randomized controlled trial" using the Boolean operator "AND" to obtain 22 documents.
After reviewing the original texts such as title, abstract, and text of these 22 papers, a total of 6 clinical papers were obtained after excluding 16 duplicate or unrelated documents.
Three randomized comparative research papers were obtained through qualitative evaluation (bias risk assessment) and used for quantitative evaluation (meta-analysis).

Table 4. Literature Retrieved with Keywords

	No. of Retrieved Studies		
Data Base	"Dementia"	AND "Acupuncture"	AND "randomized controlled trial"
PubMed	2,803	22	6
Ovid-MEDLINE	2,146	3	1
EMBASE	1,649	10	8
EBSCO Research Database	7,259	43	6
Other source	1	1	1
Total	13,858	79	22

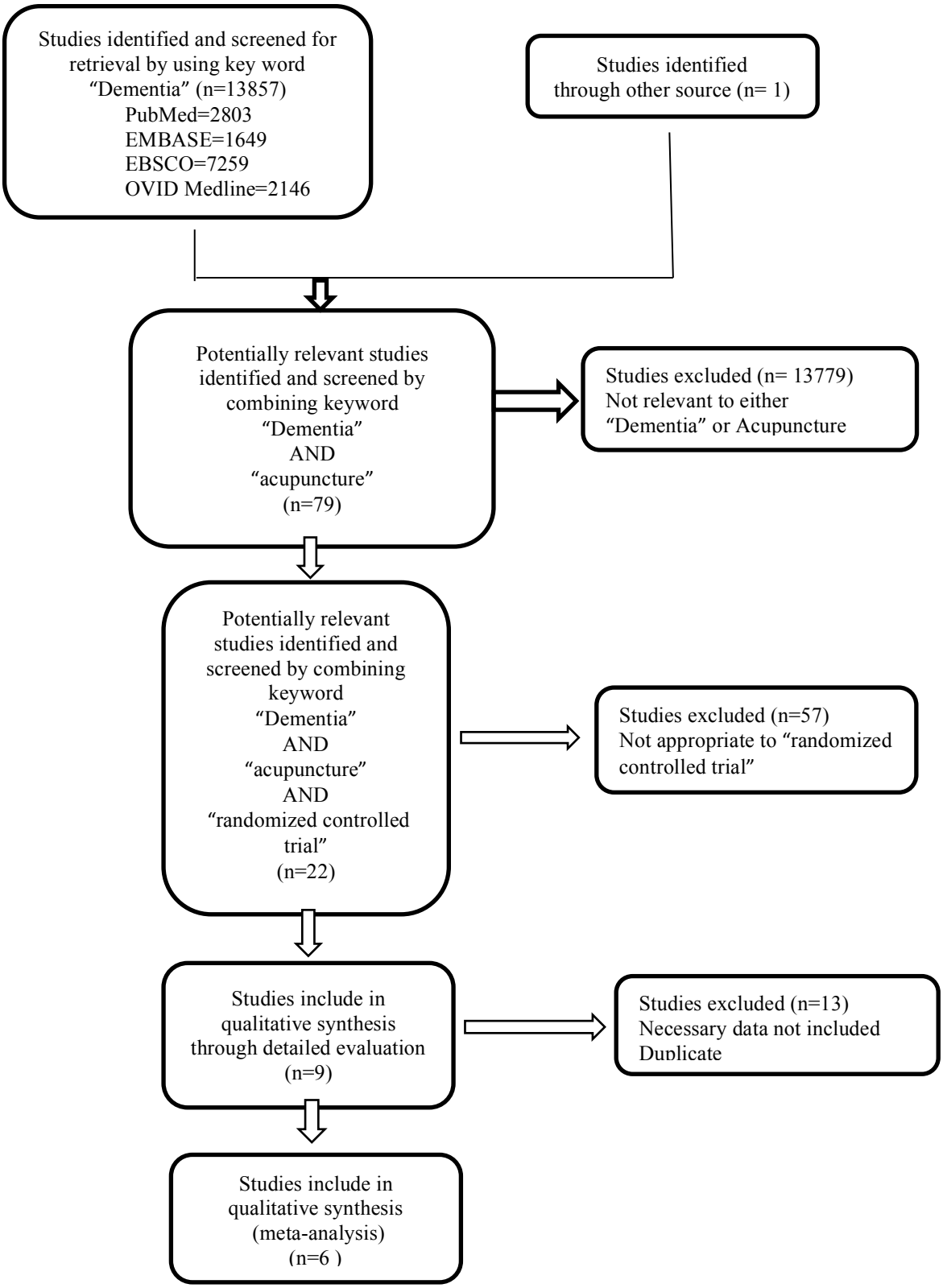

Figure 1. Flow Chart of Literature Selection

2. Data Extraction and Converting[36]

1) Extracted Data Items

In order to extract data for systematic review and meta-analysis from selected documents, research information such as study method, study subjects, comparative intervention, results and others (Table 5 to 13), were extracted according to the P-I-C-O method.

2) Conversion of the outcome data

Among the results of the data extracted from the six selected documents, Mean, Median, Standard deviation, Standard error, Odds ratio, Relative risk from the 19 items of great clinical significance were checked to derive the Mean Difference and the 95% confidence interval of the same concept for meta-analysis. (Table 5 to 13)

Table 5. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Chen2011-1[27]
Methods	Randomized Controlled Trial
Participants	"64 VD patients screened in reference to the standard for VD diagnosis in DSM-IV"
Interventions	"Chinese medicine plus rehabilitation group (32 cases) vs Western medicine group (32 cases)."
Outcomes	"MMSE score : Before treatment (18.76±4.24) After treatment (19.78±4.38) As compared with the datum before treatment, **t*=2.522, *p* <0.05 Bless Behavior Scale (BBS) Scores: Beforetreatment (19.82±4.66) After treatment (17.48±3.42) As compared with the datum before treatment, **t*=3.127, *p* <0.01."
Others	"Fund in Sci-tech Plan of Beijing Municipal Science Committee"

Table 6. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Chen2011-2[27]
Methods	Randomized Controlled Trial
Participants	"65 VD patients screened in reference to the standard for VD diagnosis in DSM-IV"
Interventions	"Chinese medicine plus acupuncture group (33 cases) vs Western medicine group (32 cases)."
Outcomes	"MMSE score : Before treatment (18.64±3.82) After treatment (19.62±3.76) As compared with the datum before treatment, **t*=2.522, *p* <0.05 Bless Behavior Scale (BBS) Scores: Beforetreatment (20.63±4.46) After treatment (17.74±3.63) As compared with the datum before treatment, **t*=3.127, *p* <0.01."
Others	"Fund in Sci-tech Plan of Beijing Municipal Science Committee"

Table 7. Data Items Being Extracted from the Selected Literature

Data Component	Data Item[27]
Literature Information	Chen2011-3
Methods	Randomized Controlled Trial
Participants	"69 VD patients screened in reference to the standard for VD diagnosis in DSM-IV"
Interventions	"Chinese medicine and acupuncture plus rehabilitation group (37 cases) vs Western medicine group (32 cases)."
Outcomes	"MMSE score : Before treatment (18.72±3.88) After treatment (20.82±4.72) As compared with the datum before treatment, **t*=2.522, *p* <0.05 Bless Behavior Scale (BBS) Scores: Beforetreatment (20.84±4.28) After treatment (17.26±3.43) As compared with the datum before treatment, **t*=3.127, *p* <0.01."
Others	"Fund in Sci-tech Plan of Beijing Municipal Science Committee"

Table 8. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Jia 2017 [28]
Methods	Randomized Controlled Trial
Participants	87 patients
Interventions	"Acupuncture vs Donepezil HCl"
Outcomes	"ADAS-cog: ADAS-cog scores showed a significant time effect (p =0.000) and time ×group interaction(p=0.000), but no group effect (p =0.235) were observed. There were significant between-group differences in ADAS-cog scores at T2 and Δ (T2-T0) (all p <0.05), but no statistical differences were found at other time points. ADCS-ADL: There were a time effect (P=0.000) were found for the ADCS-ADL23 scores analyzed using repeated measures approach, but no treatment × time interaction (p =0.421) and group effect (p =0.758) were detected. No between-group differences were found in ADCSADL23 scores at any time points, and the change scores didn't have statistical significance between the two groups"
Others	"The study was supported by National Natural Science Foundation of China and Key Project of Natural Science Foundation of Tianjin City. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript."

Table 9. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Shi2014[29]
Methods	Randomized Controlled Trial
Participants	48 Participants
Interventions	"Acupuncture vs Rehabilitation"
Outcomes	"SDSVD (Scale of Differentiation of Syndromes of Vascular Dementia) In both the random and non-random acupuncture group, patients with Kidney-essence deficiency had similar SDSVD scores at baseline and at the end of treatment. In both the non-random and combined acupuncture groups, patients with phlegm obstruction of the orifices or Liver-yang hyperactivity had significantly lower SDSVD scores at the end of treatment than at baseline. In random acupuncture group, SDSVD scores were similar at baseline and at the end of treatment."
Others	"Supported by the Program for New Century Excellent Talents in University (Ministry of Education) and the Integrated Traditional and Western Medicine Research Program (Tianjin Bureau of Public Health)"

Table 10. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Shi 2015[30]
Methods	Pragmatic Randomized Clinical Trial
Participants	48 Participants
Interventions	"Acupuncture treatment plus routine care vs Routine care"
Outcomes	"MMSE: Repeated-measures analysis of variance on MMSE scores revealed a time effect (p= 0.034) and a treatment × time interaction (p = 0.001), indicating a favorable improvement in the cognitive evolution of VaD individuals as the extension of time. No significant differences of MMSE were observed among the three groups. However, pooled-acupuncture group had significant higher score than control group (p = 0.014). ADL: There is no time effect (p = 0.241), but a treatment effect (p = 0.027) and treatment × time interaction (p = 0.014) on ADL score. Lower score was observed in the NR-acupuncture group compared to the control group (p = 0.01). Nonetheless, no significant differences were detected in R-acupuncture group versus NR-acupuncture group (p = 1.00), as well as R-acupuncture group versus control group (p = 0.067). In addition, lower score was found in pooled acupuncture group compared to the control group (p = 0.003). DEMQOL: There is a time effect (p = 0.000) and treatment × time interaction (p = 0.011) and no treatment effect (p = 0.05) on DEMQOL score, indicating a significant improvement on health-related quality of life across time. However, no significant differences were observed among the three groups. Besides, no significant differences existed between the pooled-acupuncture group and control group (p = 0.283)."
Others	"The study was supported by Program for New Century Excellent Talents in University, Technology New Star Program of Beijing, and the Bureau of Public Health of Tianjin."

Table 11. Data Items Being Extracted from the Selected Literature

Data Component	Data Items
Literature Information	Yu2006 [31]
Methods	Randomized Controlled Trial
Participants	60 patients in total with VaD
Interventions	"yi qi tiao xue fu ben pei wan" Acupuncture vs TCM Acupuncture
Outcomes	"* *p*, 0.05, significant difference between the two group; {*p*, 0.001, extremely significant difference between the two groups MMSE score (mean ¡ SD): Difference between pre- and post-treatment Treat Group (4.27 ¡ 2.05*), Control Group (2.43 ¡ 1.08) .HDS-R score (mean ¡ SD): Difference between pre- and post-treatment Treat Group (4.10 ¡ 1.15*), Control Group (2.65 ¡ 1.24) ADL score (mean ¡ SD): The score of ADL for the TG decreased from 53.93 ¡ 16.21 to 49.17 ¡ 16.10 during the treatment period (*p*, 0.001). For the CG, the score of ADL was reduced from 52.90 ¡ 16.04 to 50.67 ¡ 16.70. There was significant change in activity of daily life for either group (*p*, 0.001), but no systematic difference was observed between the two groups (*p*. 0.05)."
Others	Sources of funding: not fully described

Table 12. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Zang-2 2013 [32]
Methods	Randomized Controlled Trial
Participants	153 cases of MCI
Interventions	"Syndrome Differentiation Electroacupuncture vs Drug (nimodipine)"
Outcomes	"The score-differences in MMSE and clock drawing test in the three groups before therapy and after therapy were of obvious statistical significance(p <0.01, p <0.05). The differences before therapy and after therapy in picture recognition in the scalp electroacupuncture group and the syndrome differntiation group were of extremely satistical signigicance (p <0.01), while the differnce was not found in the drug group (p>0.05). The therapeutic effects between the scalp electroacupuncture group and the drug group, and between the syndrome differentiation group and the drug group were of statistical significant difference (p<0.05), while no statistical significance was found between the sclp electroacupuncture group and the syndrome differentiation group (p>0.05)."
Others	"Supported by the National Nature Science Foundation of China"

Table 13. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Zang 2013[32]
Methods	Randomized Controlled Trial
Participants	155 cases of MCI
Interventions	"Scalp Electroacupuncture vs Drug (nimodipine)"
Outcomes	"The score-differences in MMSE and clock drawing test in the three groups before therapy and after therapy were of obvious statistical significance(p <0.01, p <0.05). The differences before therapy and after therapy in picture recognition in the scalp electroacupuncture group and the syndrome differntiation group were of extremely satistical signigicance (p <0.01), while the differnce was not found in the drug group (p>0.05). The therapeutic effects between the scalp electroacupuncture group and the drug group, and between the syndrome differentiation group and the drug group were of statistical significant difference (p<0.05), while no statistical significance was found between the scalp electroacupuncture group and the syndrome differentiation group (p>0.05)."
Others	"Supported by the National Nature Science Foundation of China"

3. Evaluation of Risk of Bias

According to the criteria of Table # and Table#, Risk of Bias was assessed, using the RoB(Risk of Bias) software (RevMan5.3) for the evaluation of Risk of Bias about the six selected clinical trial articles. The results of Risk of Bias were shown in Table 14 to 23, and the graph of the comprehensive qualitative evaluation based on these results was illustrated in Figure 3 and 4.

Table 14. Risk of Bias Tables

Bias	2011 Chen-1	2011 Chen-2	2011 Chen-3	2017 Jia	2014 Shi	2015 Shi	2006 Yu	2013 Zhang-1	2013 Zhang-2
Random sequence generation (selection bias)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Allocation concealment (selection bias)	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Unclear Risk
Blinding of participants and personnel (performance bias)	High Risk	High Risk	High Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk
Blinding of outcome assessment (detection bias)	High Risk	High Risk	High Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Unclear Risk
Incomplete outcome data (attrition bias)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Selective reporting (reporting bias)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Other bias	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk

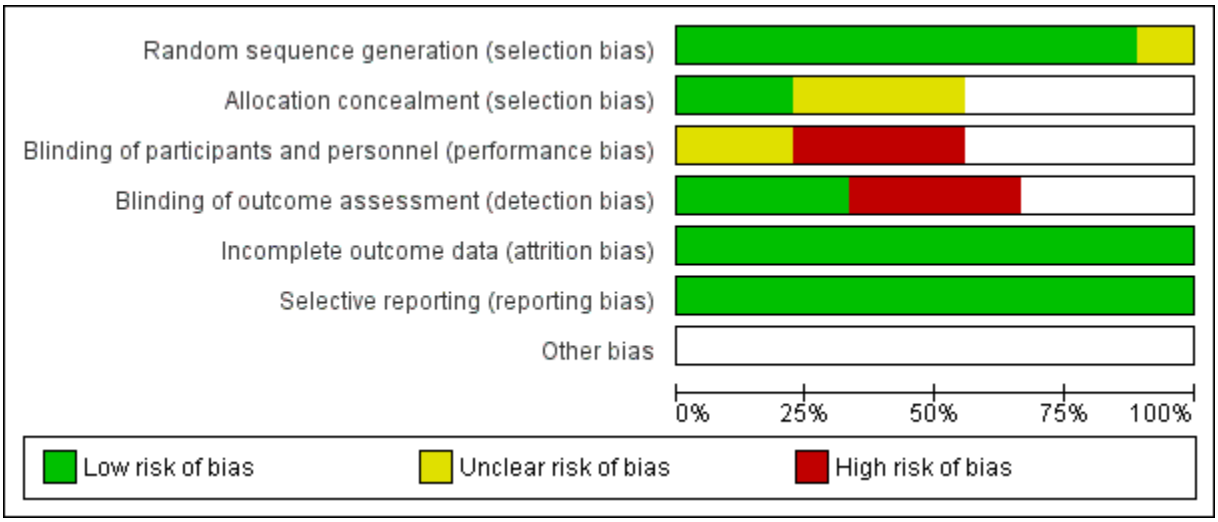

Figure 2. Risk of Bias Graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

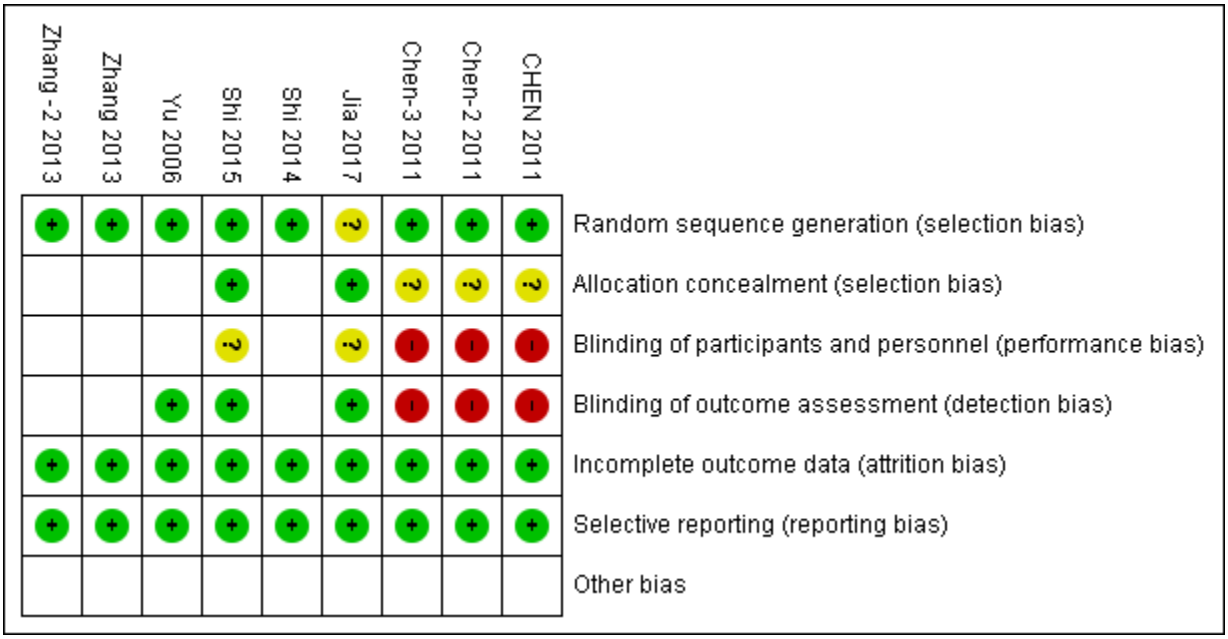

Figure 3. Risk of Bias Summary about Each Risk of Bias Item for Each Included Study.

In random assignment sequence generation, two out of nine cases (22%) were created by creating random assignment table using computer and seven cases (78%) of documents did not mention random assignment order. Two out of nine documents reported that they were distributed in an opaque envelope in the case of concealment of assignment order, and the rest documents did not mention concealment of assignment order and were unclear.

4. Analysis of heterogeneity [33]

The level of heterogeneity across the studies was estimated by overlapping CI in forest plots, and the value of the Higgin's I^2 statistics for heterogeneity test and the chi-squared test for statistical heterogeneity. The overall result of heterogeneity about studies respectively shown in Table # and the existence of heterogeneity was found (I^2 =72% >50: I^2 > 50% showed the existence of heterogeneity). In the Q-statistics, the p-value was displayed as a statistical significance level of 0.10 or higher in all ten items, and the null hypothesis was adopted, and the analysis of the fixed effect model was performed in the meta-analysis.

5. Meta-Analysis

Using the RevMan 5.3,[34] the outcome of nine subgroups in the six documents, was meta-analyzed and shown as a forest plot. (Figure 4,5)

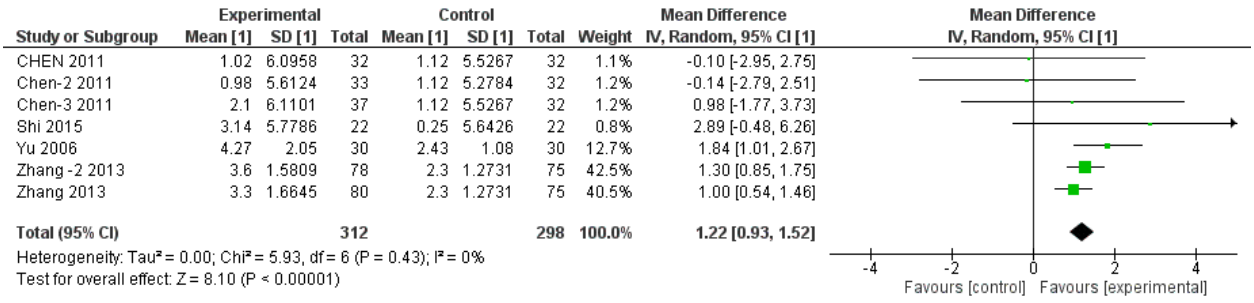

Figure 4. Forest plot of effects of acupuncture versus western treatments on dementia.

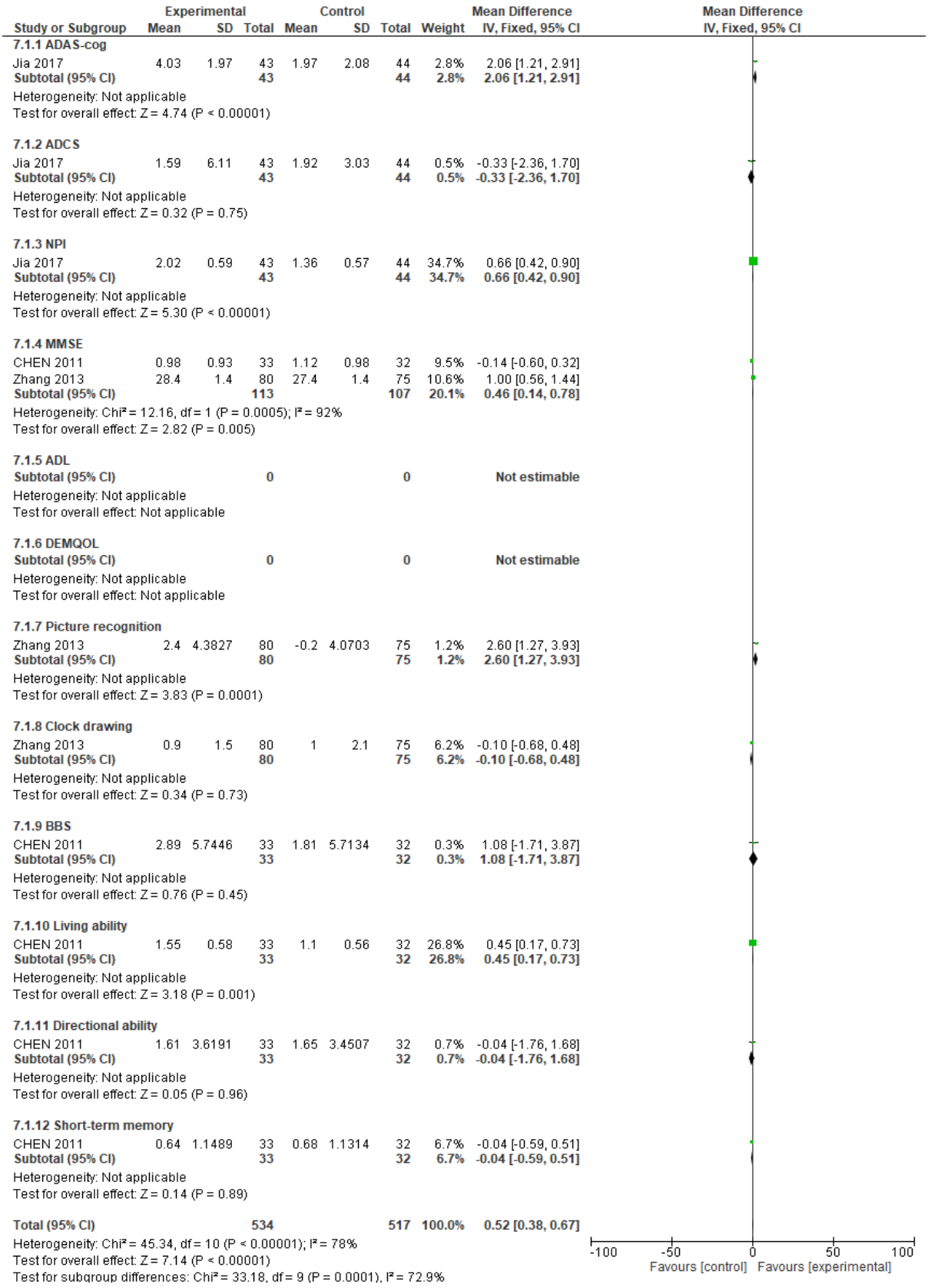

Figure 5. Forest plot of effects of acupuncture versus western treatments on dementia.

6. Identifying Reporting bias

To identify the reporting bias including publication bias, multiple publication bias, location bias, time lag bias, citation bias, outcome reporting bias, and language bias, a funnel plot of twelve outcome measures was performed preventing overestimation of summary estimates of treatment effects. All twelve items were symmetrical about the baseline, but the results were not significant because there were fewer than 10 synthesized documents.

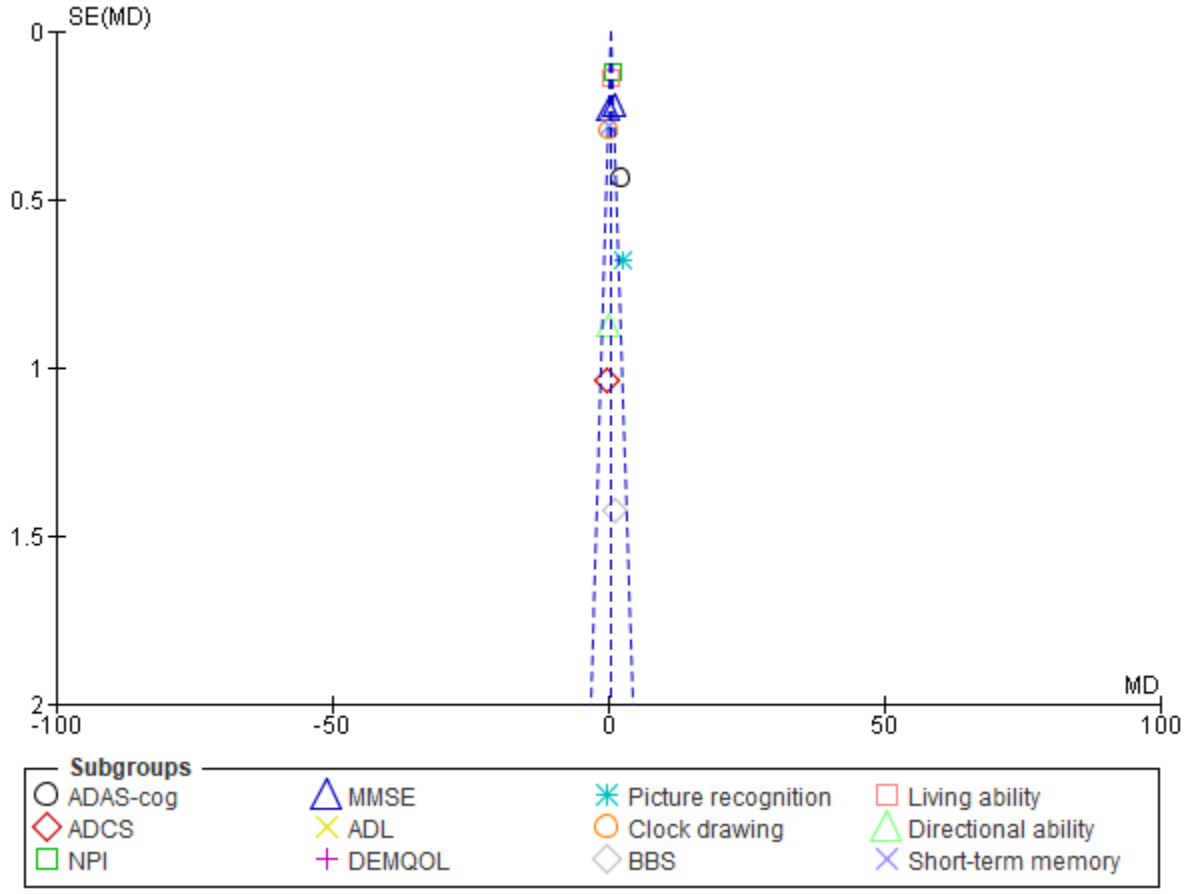

Figure 6. Funnel plot of studies included in the western treatment group.

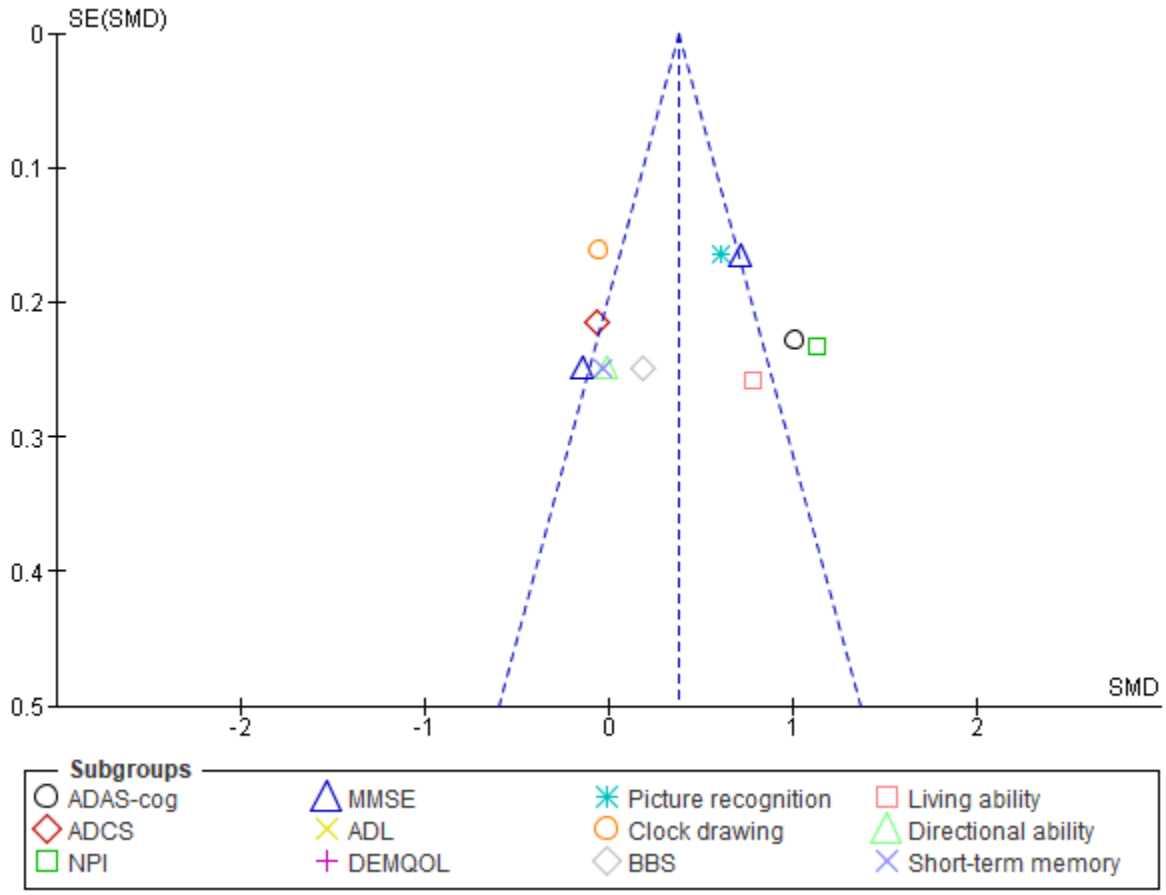

Figure 7. Funnel plot of studies included in the acupuncture group.

IV. DISCUSSION

Dementia is a chronic and progressive disease. There is currently no effective treatment for this severe disorder, and adverse events have been reported to be associated with pharmacological interventions. Acupuncture has shown to improve the cognitive function by treating patients with Dementia so the acupuncture is gradually being applied to more clinical practices. Six RCTs were contained in this meta-analysis, having a total of 632 participants that had their outcome measured using several tools such the MMSE scale, and BBS, etc. for mental issues and daily living activity.

Three RCT studies show that acupuncture increased more MMSE score compared to no treatment. Nonetheless, few RCT was not feasible for meta-analysis. Additionally, the sample size was so small as not to deliver powerful evidence. In other words, acupuncture had not powerful evidence enough to have the effect on the cognitive function of patients with dementia. The combined results of three RCTs indicated that acupuncture had more an effect on enhancing MMSE score, and acupuncture along with donepezil delivered more good result than donepezil alone in MMSE score. However, there was too little information in these three RCTs about the allocation concealment and the procedures of randomization enough to result in a high risk of selection. Additionally, only two out of the six RCTs blinded the statisticians, so that risk of bias may have been caused considerably. Latent attrition bias may result from deficient information about missing data. So, on the whole, eminent RCTs were not sufficient so to support powerful evidence. Nonetheless, among selected six RCTs, a group of two RCTs (Zhang 2013, Jia 2017) [32,28] used donepezil and trial used nimodipine that were powerfully advised by the British Association for Psychopharmacology for treating dementia. Although the drugs(piracetam) used

in one RCTs (Chen 2011) [27] had not been verified in evidence-based studies, they had been revealed to enhance cognitive function.

Furthermore, memory impairment is the core symptom of Dementia, and memory was considered as part of cognitive function. MMSE scale was most commonly applied as tools to assess cognitive function, and the improved score compared with baseline was 2.84, which is the mean MCID (a minimal clinically important difference). MMSE score of three RCTs out of the included six RCTs compared with the baseline score was improved by more than 2.93 points, and it meant the acupuncture treatment of dementia was clinically important to enhance cognitive function. Generally, the results of meta-analysis were important for clinical practice, and showed that acupuncture was more helpful than drugs to enhance the cognitive function of dementia patients and increase the action of drug named donepezil for the improvement of cognitive function in dementia patients.

Also, the symptoms of dementia were differently appeared in addition to diminishing cognitive function. According one RCT, acupuncture did not change ADL score [35], but only one RCT was not suitable for meta-analysis. Therefore, it was not sufficient to show the evidence that acupuncture had the effect on enhancing the ability of patients with dementia in daily-life-activity.

However, it can only be concluded that acupuncture may be more helpful than drug for enhancing the capability of patients with dementia to carry out daily living. Furthermore, assessment of improvement in the condition of patients with dementia as measured by other scales such as ADCS, DEMQOL, HDS, ADAS-cog, BBS and NPI was constrained by small sizes and a scant number of RCTs. This also meant that it was not enough evidence to confirm the effects of acupuncture on drugs affecting the treatment of patients with dementia. Generally, there were some difficulty in performing properly meta-analysis with diversity of symptoms and

few numbers of the effect of acupuncture treatment about the patients with dementia reported. In addition, there are some limitations of our systematic review. It is difficult to combine and classify the data owing to many kinds of outcome measurement about patients with dementia without unified tools from the characteristics of neurological patients, Besides, the diagnosis method about the dementia according the oriental medicine makes it complicated to compare the data (Shi 2014) [29] with the other data.

V. CONCLUSION

In conclusion, according to the results of meta-analysis, the acupuncture treatment may be better effective than western treatment methods, and may also enhance the effect of the current western treatment in improving the cognitive function of patients with Dementia. From the result of this study, although heterogeneity among 12 outcomes for four studies was high as many as I^2 = 74%, a total effect of acupuncture therapy on dementia provided statistical significance; SDM [95% *CI*]: 0.37 [0.14, 0.60], p = 0.002, I^2 = 74%. 11 outcomes but MMSE with three studies were evaluated with one study. Four outcomes showed significant results; ADAS-cog (1.01 [0.56, 1.45], $p < 0.0001$), NPI (1.13 [0.67, 1.58], $p < 0.00001$), Picture recognition (0.61 [0.29, 0.93]), and Living ability (0.78 [0.27, 1.29]) respectively. But eight outcomes were not statistically significant; ADCS-ADL (-0.07 [-0.49, 0.35], p = 0.75), MMSE (0.32 [-0.22, 0.87], p = 0.72, I2 = 76%), ADL (0.11 [-0.48, 0.70], p = 0.72), DEMQOL (0.52 [-0.08, 1.I^2]), Clock drawing (-0.05 [-0.37, 0.26],BBS (0.19 [-0.30, 0.67]), Directional ability (-0.01 [-0.50, 0.45]), Short-term memory (-0.03 [-0.52, 0.45]). Therefore, acupuncture treatments are overall helpful to improve the cognition, memory, living ability, and learning in cognitively uninjured or injured older adults.

In addition, acupuncture might also have more effect than drugs on enhancing the ability of daily living of patients with dementia. Moreover, acupuncture is safe for treating patients with Dementia. For forthcoming studies, the research methods such as randomization and allocation should be meticulously regulated and designed, and methodologies need to be more reported in detail. Also, more information is required about the diagnosis of dementia for future studies supported by Western and Eastern Medical Methods. A comprehensive depiction about the data veracity and the management of missing data should be demanded. Finally, well-designed trials

with considerable sample sizes was indispensable to supporting reliable evidence having an effect on the acupuncture treatment about the dementia.

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Appendix I

1. Q statistics

$$Q = \sum_{k}^{i=1} W_i (Y_i - M)^2 \quad \textbf{(1)}$$

$$Q = \sum_{k}^{i=1} W_i Y_i^2 - \frac{(\sum_{k}^{i=1} W_i Y_i)^2}{\sum_{k}^{i=1} W_i} \quad \textbf{(2)}$$

(W_i : the weighting factor the i th study ($1/V_i$), Y_i: the effect sizd for the i th study, M: summary estimate (common intervention effect), k: number of studies)

2. Higgin's I^2 statistics

$$(\%) \quad I^2 = \frac{Q - df}{Q} \times 100 \quad \textbf{(3)}$$

(Q: Q statistics, df: degree of freedom)

3. Weights in the fixed effect model (inverse variance).

$$weight = \frac{1}{variance_{withinsubject}} \quad \textbf{(4)}$$

4. A fixed-effect meta-analysis using the inverse-variance method calculates a weighted average as

$$\text{Generic inverse-variance weighted average} = \frac{\sum Y^i (1/SE_i^2)}{\sum (1/SE_i^2)} \quad \textbf{(5)}$$

(Yi: Intervention effect estimated in the *i* th study, SEi : Standard error of that estimate, the summation: across all studies)

5. Inverse-variance of Odds Ratio

$$var(lnOR) = (\frac{1}{S_E} + \frac{1}{F_E}) + (\frac{1}{S_C} + \frac{1}{F_C}) \quad \textbf{(6)}$$

6. Invers-variance of Relative Risk

$$var(lnRR) = (\frac{1}{S_E} - \frac{1}{N_E}) + (\frac{1}{S_C} - \frac{1}{N_C}) \quad \textbf{(7)}$$

7. Inverse-variance of Risk Difference

$$var(lnRD) = \frac{S_E F_E}{(S_E + F_E)^3} + \frac{S_C F_C}{(S_C + F_C)^3} \quad \textbf{(8)}$$

(S_E: Number of events in the intervention group (success), F_E: Number of events not occurring in the intervention group (failure), N_E: Total number of intervention groups, S_C: number of events in the comparison group (success), F_C: number of events in the comparison group (failure), N_C: total number of comparison groups)

8. The weighted average in the Random-effects model del

$$WMD_{summary} = \frac{weight_i \times mean_i}{weight_i} \quad \textbf{(9)}$$

($WMD_{summary}$: Summary of weighted deviation, $weight_i$: The weight in the *i* th study, $mean_i$: mean in the *i* th study)

$$mean_i = mean_E - mean_C \quad \textbf{(10)}$$

($mean_E$: mean in the intervention group, $mean_C$: mean in the comparative group)

$$weight_i = \frac{1}{variance_i} = \frac{1}{SD^2} \quad \textbf{(11)}$$

$$95\%CI = mean_S \pm (1.96 \times \sqrt{variance_S}) \quad \textbf{(12)}$$

$$variance_S = \frac{1}{\sum weight_i} \quad \textbf{(13)}$$

(variance$_i$: variance in *i*-th study, SD: standard deviation of integrated estimates, mean$_S$: mean of summary estimates, variance$_S$: variance of summary estimate mean)

9. Standardized Mean Difference (SMD) for Random-effects model

$$SMD_{summary} = \frac{weight_i \times SMD_i}{weight_i}. \quad \textbf{(14)}$$

(SMD$_{summary}$: summary value of standardized mean difference, weight$_i$: weight in *i*-th study, SMD$_i$: standardized mean difference in *i*-th study)

$$SMD_i = \frac{Difference\ in\ mean\ outcome\ between\ groups}{Standard\ deviation\ of\ outcome\ among\ participants}. \quad \textbf{(15)}$$

$$weight_i = \frac{1}{variance_i} = \frac{2 \times N_i}{8 + SMD_i^2} \quad \textbf{(16)}$$

$$95\%CI = SMD_S \pm (1.96 \times \sqrt{variance_S}) \quad \textbf{(17)}$$

$$variance_S = \frac{1}{\sum weight_i} \quad \textbf{(18)}$$

(variance$_i$: variance in *i*-th study, SD: standard deviation of integrated estimates, variance$_S$: variance of standardized estimates)

10. Cohen's *d* value

$$d = \frac{\bar{x}_1 - \bar{x}_2}{s}. \quad \textbf{(19)}$$

Appendix II

Table A-1 Mini Mental State Examination (MMSE)

Category	Possible points	Description
Orientation to time	5	"From broadest to most narrow. Orientation to time has been correlated with future decline."
Orientation to place	5	"From broadest to most narrow. This is sometimes narrowed down to streets, and sometimes to floor."
Registration	3	"Repeating named prompts"
Attention and calculation	5	"Serial sevens, or spelling "world" backwards. It has been suggested that serial sevens may be more appropriate in a population where English is not the first language."
Recall	3	"Registration recall"
Language	2	"Naming a pencil and a watch"
Repetition	1	"Speaking back a phrase"
Complex commands	6	"Varies. Can involve drawing figure shown."
"Any score greater than or equal to 24 points (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment. The raw score may also need to be corrected for educational attainment and age. That is, a maximal score of 30 points can never rule out dementia. Low to very low scores correlate closely with the presence of dementia, although other mental disorders can also lead to abnormal findings on MMSE testing."		

Table A-2. Hasegawa's Dementia Scale-Revised(HDS-R)

Question 1 (Age)	Give one point to the answer made correctly or within a deviation of 2 years.
Question 2 (Orientation in time)	the examiner may ask about the year, month, day and the day of the week either at the same time or slowly one by one. Give one point to each correct answer.
Question 3 (Orientation in place)	Give two points to a spon1aneous correct answer. It is judged to be correct if the subject substantially understands where he/she is, although he/she cannot exactly say the name and address of the hospital, the office or his/her house where he/she is now. If a correct answer cannot be gotten, ask the subject 5 seconds later: "Is this a hospital, or office or your house?" Give one point to a correct answer.
Question 4 (Repeating 3words)	Pronounce the three words slowly one by one. After that, ask the subject to repeat them. Give one point to each correctly repeated word. If a word cannot be correctly repeated, teach at least three times what it is and ask the subject to memorize it. But, if this process ends up with a failure, delete the word delayed recall in Question 7.
Question 5 (Serial subtractions of 7s)	The first question is "subtract 7 from 100". If the answer is correct, give one point to it and proceed to the second question. If the answer is incorrect, discontinue this question and proceed *to* next question 6. In second question, do not repeat the correct answer made by the subject to the first question, such as "subtract 7 from 93". If the answer is correct, give one point to it.
Question 6 (Digits backward)	Frist, pronounce 3 digits, 6-8-2, slowly at intervals of one second. After that, ask the subject *to* repeat them backward. If the subject can do this correctly, give one point to the success and proceed to the next. If this ends up with a failure, discontinue this question and proceed to the next Question 7. Second, pronounce 4 digits, 3-5-2-9, in the same manner as above. After that, ask the subject to repeat them backward. If the subject can do this correctly, give one point to the success.
Question 7 (Recalling of 3 words)	Recall 3 words in Question 4. Give two points to each spontaneous answer. If the subject cannot well recall word, give him/her such hints as "a plant" for cherry blossom, "an anin1al" for cat and "a vehicle" for tram after a short interval 1ime. Do not convey two or more hints at a 1ime; instead, convey them one by one confirming the subject's response. For Example, if the subject cannot remember both "cherry blossom" and "tram", say to him/her, "one was a plant, wasn't it?" If he/she can correctly recall "cherry blossom", give one point to the success. Shortly after, convey a hint to him/her saying, "the other was a vehicle, wasn't it?" If he/she can correctly reproduce "tram", give one point to the success.
Question 8 (Recalling 5 objects)	Five objects must be ready for use. They are optional, but must be unrelated common objects as in a combination of a watch, a key, a cigarette, a pen and a coin. Put the five objects on the table one by one, calling their names, then take them back and ask for recall. Give one point to each correct answer, regardless of the order of recall.
Question 9	Enter in the given space the names of the vegetables the subject calls and avoid double

(Generating vegetables)	entries. Since this question is intended to observe generating fluency, discontinue the question if the name of the first or subsequent vegetable is not called for 10 seconds. Give 0 point to 0-5 vegetable (s), and for each vegetable name after the 5th one, give to 1 point each.
Any score greater than or equal to 20 points (out of 30) indicates a normal cognition.	

Table A-3. Risk of Bias from Chen2011-1

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Allocation concealment (selection bias)	Unclear risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Blinding of participants and personnel (performance bias)	High risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Blinding of outcome assessment (detection bias)	High risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Incomplete outcome data (attrition bias)	Low risk	Table 1, 2, 3 [27]
Selective reporting (reporting bias)	Low risk	Table 1, 2, 3[27]
Other bias	Unclear risk	

Table A-4. Risk of Bias from Chen2011-2

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Allocation concealment (selection bias)	Unclear risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Blinding of participants and personnel (performance bias)	High risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Blinding of outcome assessment (detection bias)	High risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Incomplete outcome data (attrition bias)	Low risk	Table 1, 2, 3[27]
Selective reporting (reporting bias)	Low risk	Table 1, 2, 3[27]
Other bias	Unclear risk	

Table A-5. Risk of Bias from Chen 2011-3

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Allocation concealment (selection bias)	Unclear risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Blinding of participants and personnel (performance bias)	High risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Blinding of outcome assessment (detection bias)	High risk	"Total 134 VD patients were randomly divided into a Chinese medicine plus rehabilitation group (32 cases), a Chinese medicine plus acupuncture group (33 cases), a Chinese medicine and acupuncture plus rehabilitation group (37 cases and a Western medicine group (32 cases)."
Incomplete outcome data (attrition bias)	Low risk	Table 1, 2, 3[27]
Selective reporting (reporting bias)	Low risk	Table 1, 2, 3[27]
Other bias	Unclear risk	

Table A-6. Risk of Bias from Jia 2017

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"After the baseline, all patients were randomly allocated into either AG or DG in a ratio of 1:1 by a computer-generated, randomly location sequence (random list generated with SPSS 13.0)"
Allocation concealment (selection bias)	Low risk	"The random number table was sealed in a special envelope."
Blinding of participants and personnel (performance bias)	Unclear risk	"physicians could not be blinded due to the nature of the intervention. The acupuncturists had to know the group assignment because of manipulation."
Blinding of outcome assessment (detection bias)	Low risk	"Data collection was performed by 2 blinded evaluators. Blinding was also maintained for data analysis."
Incomplete outcome data (attrition bias)	Low risk	"Eight (9.19%) out of 87 patients dropped out during the trial, one patient stopped the treatment due to fracture, one patient died from heart attacks, four patients could not tolerate donepezil for SAEs, one patient withdrew owing to the change of address, and one patient lost at the follow-up. A total of 79 patients (90.80%) completed the entire treatment and follow-up processes, 40 (93.02%) in the AG and 39(88.64%) in the DG."
Selective reporting (reporting bias)	Low risk	"Eight (9.19%) out of 87 patients dropped out during the trial, one patient stopped the treatment due to fracture, one patient died from heart attacks, four patients could not tolerate donepezil for SAEs, one patients withdrew owing to the change of address, and one patient lost at the follow-up. A total of 79 patients (90.80%) completed the entire treatment and follow-up processes, 40 (93.02%) in the AG and 39(88.64%) in the DG."
Other bias	Unclear risk	

Table A-7. Risk of Bias from Shi 2014

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients who agreed to randomization were randomly assigned to the random acupuncture or guided rehabilitation group by using a computer-generated, blocked random-allocation sequence with a block size of 6 (SAS software, Cary, NC, USA)."
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Low risk	"One patient in the random acupuncture group had a subsequent recurrence of stroke, and another patient discontinued treatment halfway through the study. These patients were therefore not included in the data analysis. Two patients of the guided rehabilitation group were subsequently lost to follow-up (one moved to another location and the other died of myocardial infarction). A total of 63 patients (random acupuncture group: 22, guided rehabilitation group: 22, non-random acupuncture group: 19) were included in the data analysis."
Selective reporting (reporting bias)	Low risk	"One patient in the random acupuncture group had a subsequent recurrence of stroke, and another patient discontinued treatment halfway through the study. These patients were therefore not included in the data analysis. Two patients of the guided rehabilitation group were subsequently lost to follow-up (one moved to another location and the other died of myocardial infarction). A total of 63 patients (random acupuncture group: 22, guided rehabilitation group: 22, non-random acupuncture group: 19) were included in the data analysis."
Other bias	Unclear risk	

Table A-8. Risk of Bias from Shi 2015

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Block randomization with a block size of 4 was by sequential, sealed, opaque envelopes. It occurred after the acupuncturist's evaluation (concealed allocation) using a computer-generated, random-allocation sequence (random list generated with SAS 8.2)."
Allocation concealment (selection bias)	Low risk	"Block randomization with a block size of 4 was by sequential, sealed, opaque envelopes. It occurred after the acupuncturist's evaluation (concealed allocation) using a computer-generated, random-allocation sequence (random list generated with SAS 8.2)."
Blinding of participants and personnel (performance bias)	Unclear risk	"The acupuncturists were not blinded to the treatments they delivered because acupuncture manipulation made this impossible. During the intervention, acupuncturist and the personnel who collected data were segregated by an opaque screen immediately after the treatment started and were instructed not to exchange information with each other."
Blinding of outcome assessment (detection bias)	Low risk	"We ensured that the patients, data collection staff, and data analysts were blinded during the study period; they were all unaware of the randomization."
Incomplete outcome data (attrition bias)	Low risk	"Five patients dropped out during the trial, accounting for a 7.4% dropout rate. Among the 5 dropouts, 1 patient had recurrent stroke, 1 patient died because of heart attacks, 2 patients did not tolerate needling, and 1 patient withdrew due to move from one city to another. Thus, the protocol analysis included 63 patients."
Selective reporting (reporting bias)	Low risk	"Five patients dropped out during the trial, accounting for a 7.4% dropout rate. Among the 5 dropouts, 1 patient had recurrent stroke, 1 patient died because of heart attacks, 2 patients did not tolerate needling, and 1 patient withdrew due to move from one city to another. Thus, the protocol analysis included 63 patients."
Other bias	Unclear risk	

Table A-9. Risk of Bias from Yu 2006

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Sixty inpatients with VaD were randomly assigned to the treat group (TG) or control group (CG)."
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	"Both the patients and examiner were blinded as to which group the patients belonged to. The subjects did not know that some were given a control treatment, and they were thus blinded to the kind of treatment they received. The acupuncturists knew what kind of treatment each subject was given, and the study was thus single blinded in that respect. The physician examining the patients and carrying out the measurements of the MMSE, HDS-R and ADL exams was unaware of what kind of treatment each subject received. That part of the study was thus double blinded"
Blinding of outcome assessment (detection bias)	Low risk	"The statistician who performed the analysis was blinded to groups and treatments"
Incomplete outcome data (attrition bias)	Low risk	"There were no dropouts during the treatment period. Data on the subjects with respect to general characteristics were shown in Table 1"
Selective reporting (reporting bias)	Low risk	"There were no dropouts during the treatment period. Data on the subjects with respect to general characteristics were shown in Table 1"
Other bias	Unclear risk	

Table A-10. Risk of Bias from Zang 2013

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"According to the inclusion and exclusion criteria, the patients were randomly divided into the drug group, the scalp electroacupuncture group and the TCM syndrome differentiation group."
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Low risk	Table 1, 2, 3, 4[32]
Selective reporting (reporting bias)	Low risk	Table 1, 2, 3, 4[32]
Other bias	Unclear risk	

Table A-11. Risk of Bias from Zang-2 2013

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"According to the inclusion and exclusion criteria, the patients were randomly divided into the drug group, the scalp electroacupuncture group and the TCM syndrome differentiation group"
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Low risk	Table 1, 2, 3, 4[32]
Selective reporting (reporting bias)	Low risk	Table 1, 2, 3, 4[32]
Other bias	Unclear risk	