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The Effect of Alternative Medicine on Quality-of-Life Outcomes for Dementia Patients: A Systematic Review and Meta-Analysis

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Objectives: As effective treatments for dementia are lacking in Western medicine, complementary and alternative medicine (CAM) is considered a useful option. While the quality of life (QoL) is a vital outcome for patients with dementia, the QoL of patients receiving CAM for dementia remains ambiguous. This study aimed to determine the effect of CAM on QoL outcomes in dementia patients.

Methods: A search was performed using the keywords "dementia," "Alzheimer's," "cognitive impairment," "Chinese," "Korean," "oriental," "herbal," "acupuncture," and "quality of life". All quantitative data were synthesized using R version 4.1.1.

Results: Twenty-five randomized controlled trials (RCTs), 16 pre-post trials, and two cohort studies were selected for the systematic review. QoL in Alzheimer's disease (QOL-AD) (n=11, 25.6%) and geriatric QoL in dementia (GQOL-D, n=9, 20.9%) were the most utilized QoL instruments. Significant benefits in QoL were observed after receiving mind, body, combined mind and body, nursing, oriental medicine, and acupuncture therapies. In the meta-analysis, the combined effect was shown to significantly increase QOL-AD compared to before CAM interventions (standardized mean difference, SMD: 0.507; 95% confidence interval (CI), 0.191 ~ 0.824; p<0.01). The overall synthesized estimates in the GQOL-D showed a significantly improved QoL (SMD: 0.537, 95% CI: 0.238 ~ 0.837 p<0.01; one group; SMD: 1.465, 95% CI: 0.934 ~ 1.996, p<0.01). The seven studies assessing the cost-effectiveness of CAM reported uncertain outcomes.

Conclusions: This study showed that CAM interventions benefited patients with dementia by improving their QoL. While additional standardized research is required, CAMs are suggested as effective clinical management for patients with dementia. They are also suggested as complementing therapies for these patients.

Key Words: Dementia, Complementary and alternative medicine, Quality of life, Systematic review, Meta-analysis.

I. INTRODUCTION

In 2020, the approximately 55 million people were living with dementia worldwide. With a globally aging population, it is projected to reach 82 million by 2030 and 153 million by 2050[1]. In the United States, the cost of healthcare, long-term care, and hospice services for people with dementia aged 65 years and older was estimated to be US$305 billion in 2020[2]. The global economic cost of dementia is projected to reach US$2 trillion by 2030[3].

In Japan, which is well-known for being the most aged country in the world, the number of dementia patients aged 65 years and over is 6.02 million, as of 2020 (16.7% of total population are aged 65 years and over). This is expected to reach 7.97 million (21.1% of the total population aged 65 years and over) by 2050[4]. In Korea, where the population aging rate is faster than that in Japan[5], the number of dementia patients aged 65 years or over (83000 in 2020, which is 10.3% of the total population aged 65 years and over) is expected to exceed three million (15.2% of the total population aged 65 years and over) by 2050. The societal costs of dementia are expected to increase from US$10 billion in 2013 to US$37 billion in 2050[6,7].

Alzheimer's disease (AD), which is the most common form of dementia, accounting for 60%~70% thereof, is a representative disease that lowers patients' and their caregiver's quality of life (QoL)[8,9]. However, most currently used prescription medicines only maintain one's cognitive or functional state to reduce the deterioration of memory loss in patients with AD or dementia[10]. Due to a lack of effective dementia treatments, reducing the economic burden and enhancing QoL of patients or caregivers a high priority[11-13].

Another option for the treatment of dementia patients in consideration of a deteriorating QoL and disease progression may be complementary and alternative medicine (CAM) therapies. The National Institute of Health (NIH) defines CAM by describing the concepts behind the terms: "complementary" means that non-mainstream practice is used with conventional therapy and "alternative" means that it is used as a substitute for conventional therapy[14]. Considering that CAM may be used more frequently in diseases in which a conventional treatment regimen is not clearly established, CAM treatments may be particularly attractive to patients with dementia. The symptoms and prognosis of dementia differ between individual patients, and the mental status of patients widely varies[15]. In CAM therapy, individual patient's genetic and environmental factors are usually considered for a more individualized treatment or management program[16].

Donepezil (an acetylcholinesterase inhibitor) is the most commonly used medicine to treat AD and relieve the symptoms of dementia[17]. Its side effects include nausea, diarrhea, malaise, and dizziness; as acetylcholine is also located elsewhere in the body[17,18]. There is constant debate regarding the effect of a CAM intervention for dementia patients in the past[19]. In several studies, some CAM therapies' clinical effect has been compared with conventional therapy for dementia, such as donepezil[20-23]. For example, Chinese herbal medicine or cognitive-communication stimulation, in addition to conventional treatment with donepezil, seem superior to monotherapy. It may provide an additive treatment effect for AD[20,22,24]. Furthermore, acupuncture as a monotherapy for AD has demonstrated superior clinical effects in patients treated with donepezil[21].

Multiple studies regarding CAM's effects on dementia have examined and reported the efficacy and safety outcomes thereof through case studies or observational study designs, rather than within rigorous randomized controlled trial (RCT) designs[25,26]. This is

because there are various types of CAM therapies that can be applied to patients with dementia. Unlike in conventional medicine, each treatment is usually tailored to the individual patient's requirements due to the nature of the CAM treatment rather than it being provided as a uniform regimen to patients[27]. It has also been noted that the lack of an adequate impact evaluation instrument to assess its clinical effects make it challenging for CAM studies to provide relevant and valid evidence[28].

Evidence of QoL or cost-effectiveness outcomes is required to inform decision-makers and payers in the process of resource allocation decision-making in the evidence-based medicine milieu. Since 1997, health insurance companies have covered CAM therapies in Washington, DC[29]. In Germany, some CAM treatments, such as physiotherapy, chiropractic, phytotherapy, and acupuncture are covered by German statutory health insurance (SHI)[30]. For reimbersement by the SHI, the therapist must obtain the corresponding CAM qualifications[30].

A decline in cognitive function affects the patients' QoL with dementia according to their disease progression[31]. Considering the entire system of the care approach with CAM interventions, QoL measures, which assesses a more expanded and comprehensive spectrum of treatment effects, may be more appropriate to examine the health outcomes of CAM. This is as compared to other clinical outcome measurement tools evaluating a single aspect of clinical effectiveness. Widely used methods for QoL measurement are the European Five-Dimensional Quality of Life Scale (EQ-5D), Quality of Life Assessment Short Form (SF-36), and World Health Organization Quality of Life (WHOQOL). These have been validated and utilized in the general population[32]. However, it may not be useful or viable for assessing QoL in patients with cognitive impairment, such as dementia. As these indicators are measured through subjective self-reporting on questionnaires, there may be obstacles in behavioral or cognitive expression for patients with severe dementia. This causes a decline in the credibility of the subjective information on the efficacy of the CAM intervention. Therefore, dementia-specific measures assessing cognitive functioning and QoL have been developed and utilized as follows: Dementia Quality of Life (DEMQOL)[33] and the Alzheimer's disease-related quality of life scale (QoL-AD)[31,34]. These measures have both patient and proxy forms, which a family or professional clinician fills out on behalf of the patients. Therefore, they are suitable for use across a range of severity[31].

In recent years, several systematic review (SR) studies on dementia have been conducted to combine existing studies evaluating the QoL improvement of CAM interventions. These include aromatherapy[35], Chinese herbal medicine[36], and psychological intervention[37,38] or cost-effectiveness of exercise, cognitive, or psychological interventions[39]. Previous SRs were conducted in China[35,36,38], the UK[37] and Germany[39]. However, these SR studies omitted other important CAM interventions, such as Chinese or oriental medicine or acupuncture, which are utilized in Asia. Previous SR studies on Chinese herbal medicines included only Chinese studies. Furthermore, few studies have examined the overall QoL improvement or cost-effectiveness competitiveness of a variety of CAM interventions such as acupuncture for dementia, as compared to modern CAM therapy.

In this study, we systematically reviewed previously published articles that studied the effectiveness of all types of CAM therapies for dementia to determine QoL and cost-effectiveness outcomes through meta-analysis.

II. METHODS

1. Criteria for inclusion and exclusion

Based on the keywords regarding patients (P), interventions (I), and outcomes (O), the following literature was searched and drawn: focusing on (1) AD, vascular dementia (VaD), overall dementia, and mild cognitive impairment (MCI); considering (2) oriental medicine interventions including Chinese medicine, acupuncture, or cognitive behavior programs; and (3) examining outcomes related to one's QoL, utility, and cost. We included all types of dementia and some studies had focused on a subtype of dementia. When the study did not classify the subtype, we categorized it as dementia. The primary outcomes are QoL outcomes and secondary outcomes are cost-effectiveness outcomes.

2. Literature searches

We searched the literature published from their inception to December 2019, using the following databases: MEDLINE, PubMed, EMBASE, Cochrane Central, CiNii, CNKI, KMbase, KISS, NDSL, RISS, and OASIS. The keywords we used in search process were: "Dementia" or "Alzheimer's" or "Cognitive impairment" or "Cognitive dysfunction" and "Complementary and alternative medicine" or "Chinese" or "Oriental" or "Korean" or "Herb" or "Acupuncture" and "Quality of life" or "Cost" or "Econom*" or "Utility." We also searched for additional literature published between 2020 and 2021, using the same databases.

3. Data selection

Two authors independently evaluated and selected studies in two steps: First, studies unrelated to the keywords were excluded by reviewing titles and abstracts. Abstracts without full texts, news articles, books, and non-clinical trial studies were not considered. Thereafter, based on the full text, we determined the final list according to the inclusion and exclusion criteria. The full text of Chinese papers were translated and evaluated by a bilingual research assistant.

4. Data extraction

Data from each article were extracted from the selected studies and organized in an Excel file. It specified the authors' names, publication years, titles, journal names, study types (RCT or non-RCT), number and types of patients, and types of CAM interventions. Data extraction was independently performed by two researchers, and any differences were resolved by a discussion with a third author.

5. Quality/risk of bias assessment of included studies

The risk of bias (RoB) for all included studies was also examined by two independent researchers using two Cochrane Collaboration tools: ROB for assessing the quality of the RCT articles selected for the SR[40] and Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) for non-RCTs[41]. The evaluation of the bias was reported in the format "low, high, or unclear."

6. Data analysis

We reviewed and synthesized the QoL and cost-effectiveness outcomes of the CAM by classifying the selected articles according to the QoL instrument type and dementia disease type. Meta-analysis were performed to combine the quantitative data from the multiple studies with quantitative estimates reported, which used distinct QoL instruments. The meta-analysis were performed using R (version 4.1.1; Biostat, Englewood, NJ). The standardized mean difference (SMD) values of the QoL estimates were assessed and tested at a statistical significance level of 5%. The

protocol of this systematic review was not registered on the International Prospective Register of Systematic Reviews (PROSPERO) database. It is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

III. RESULTS

1. Study characteristics

The study selection process for the systematic analysis is described in Fig. 1. A total of 3427 articles were retrieved at the commencement of the search process. After removing the duplicate articles and screening titles and abstracts according to the criteria, 541 articles were selected as potentially relevant studies. Among them, 458 were deemed ineligible due to: the absence of complementary interventions (n=319), having no clinical outcomes (n=71), the unavailability of the full text (n=36), not being a clinical trial (n=27), and not containing patients with dementia (n=5). Of the 83 articles remaining, 56 full-text articles were excluded because the QoL results were not reported (n=27), CAM interventions were absent (n=21), and participants were not dementia patients but rather the caregiver population (n=8). We added eight articles via the snowballing technique, such as via the pursuing of references of references[35-37,42-44] and eight articles from an additional search from 2020~2021[45-52]. Finally, 43 articles satisfying all the inclusion criteria were selected for the systematic analysis. Among these, 25 articles contained quantitative QoL outcome measures and were included in the meta-analysis.

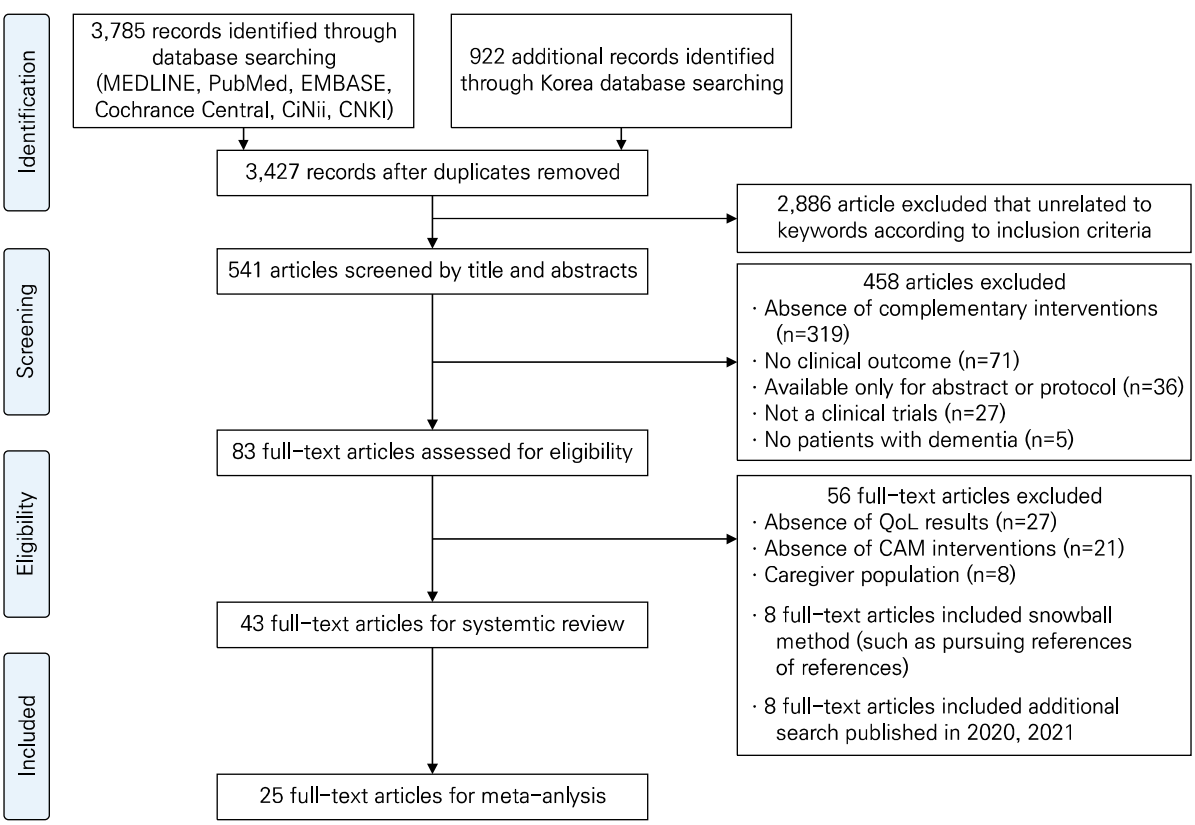

Fig. 1. Flow chart of study selection.

The main characteristics of the 43 studies are summarized in Table 1. All the studies were published between 2006 and 2021. Most papers were RCTs (n=25, 58.1%)[45,48,49,53-74]. The remainder were prospective pre-post comparison studies without a specific intervention for the comparison group (n=16, 37.2%)[46,47,50-52,75-85] and retrospective cohort-designed studies (n=2, 4.7%)[86,87]. Among the 43 studies, 48.8% were published in English (n=21)[45,46,49,51,52,55,56,60-63,65,66,68-70,75,79,82,84,86], 34.9% in Korean (n=15)[47,48,50,53,54,58,59,67,76-78,80,81,83,85], and 16.3% in Chinese (n=7)[57,64,71-74,87]. The studies were conducted in eight countries from Asia (n=35, 81.3%) and Europe (n=8, 18.6%). Most of the research were conducted in Korea (n=20, 46.5%)[47-50,53,54,58-61,63,67,76-81,83,85] and China (n=11, 25.6%)[45,46,52,57,64,71-74,82,87] followed by the United Kingdom (n=4, 9.3%), and so on. The study's duration (treatment or follow-up) ranged from three days to three years. The most frequent treatment duration was 12 weeks (n=11, 25.6%).

The disease types considered in these studies were dementia (n=19, 44.2%), MCI (n=11, 25.6%), AD (n=6, 14.0%), VaD (n=3, 7.0%), senile dementia (n=2, 4.7%), AD plus MCI (n=1), and AD plus VaD (n=1). CAM interventions were classified into seven categories according to the Johns Hopkins medicine classification[88]: (1) body plus mind; (2) mind; (3) body; (4) nursing; (5) acupuncture; (6) Chinese or oriental medicine; and (7) sense therapy. Among the 43 articles, sole mind therapy (n=15, 34.9%) was the most frequently examined intervention, followed by body plus mind (n=11, 25.6%) and sole body therapy (n=8, 18.6%). The mind intervention covered cognitive therapy, meditation, art therapy, sense, and biofeedback. Specific interventions in the body intervention category included exercise or physical activity. Three studies (7.0%) were related to a nursing intervention. Traditional oriental CAM, which included acupuncture (n=3, 7.0%), oriental medicine (n=2, 4.7%), and acupuncture plus mind (n=1, 2.3%), was examined in six studies.

Various QoL measurements were used to examine the effects of CAM interventions in patients with dementia. A total of 55.8% of the studies (n=24) utilized disease-specific QoL measurement as follows: QoL-AD (n=11, 25.6%)[46,48,50,57,60,61,63,66,75,78,85], Geriatric Quality of Life-Dementia (GQOL-D) (n=9, 20.9%)[47,49,53,54,59,79-81,83], and DEMQOL (n=2, 4.7%)[66,82], DEMQOL-proxy (n=1)[65], cognitive-impairment quality of life (CIQOL) (n=1)[87]. The general QoL measuring instruments used in 18 studies were as follows: WHOQOL derived instruments (WHOQOL-BREF; n=3[72,77,84], WHOQOL-100; n=1[74], 9.3%), Short Form Health Survey Questionnaire-36 (SF-36) (n=3, 7.0%)[58,64,71], SF-12 (n=3, 7.0%)[45,51,52], EQ-5D (n=3, 7.0%)[67,86], EQ-VAS (n=1)[49], EQ-VAS-proxy (n=1)[70], 15D (15-dimensional, standardized, self-administered measure of health-related quality of life) (n=1)[62], life satisfaction index-A (LSI-A) (n=1)[76], and Physical Quality of Life Index (PQLI) (n=1)[73].

Among the 43 final studies, 40 studies reported the QoL outcomes. Out of these, three studies reported the additional cost outcomes[49,62,87]. Seven reported cost outcomes, such as the mean cost of self-management group rehabilitation[62], incremental cost-effectiveness ratio values for cognitive therapy[55], exercise[56], and traditional Chinese medicine[87], the cost comparison between the exercise group and community care[68], and supportive interventions such as the quality-adjusted life-year (QALY)[89].

2. Quality/risk of bias of included studies

The risk assessment of RCT papers using the Cochrane's RoB tool's results are summarized in Fig. 2. Most studies were assessed as having a "low-risk" bias regarding random sampling, except for two studies[59,61]. Regarding the allocation concealment, 16 studies (64.1%) had a "low risk" bias, and others were

Table 1. Summary of the Articles Included in the Systematic Analysis

No	First author, year	Study design	Intervention category	Intervention		Outcome measure	Sample size		Patients	Treatment and follow-up duration (weeks)
				Treatment (TRT)	Comparison (CPR)		TRT	CPR		
1	Lee 2014	Pre/post	Body and mind	Cognitive training+physical activity, social interaction	-	GQOL	6	-	Dementia	8
2	Chew 2015	Cohort	Body and mind	MINDVital[1)]	-	EQ-5D	55	-	Dementia	8
3	Kim 2015	Pre/post	Body and mind	Experience-based group therapy	-	GQOL-D	12	-	Dementia	10
4	Kim 2016	RCT	Body and mind	Pharmacological treatment & cognitive and exercise program	Pharmacological treatment	QOL-AD	32	21	AD	24
5	Laakkonen 2016	RCT	Body and mind	Self-management group rehabilitation	Usual care	15D[2)], cost	67	67	dementia	8
6	Sung 2016	Pre/post	Body and mind	Communication, music, art therapy, physical exercise	None	GQOL-D	33	35	Dementia	10
7	Tai 2016	Pre/post	Body and mind	Multiple training modalities (Tai Chi, calligraphy, drawing)	Routine activity	WHOQOL-BREF	14	10	AD	6
8	Yoon 2016	Pre/post	Body and mind	Cognitive and physical activity Occupational therapy program	-	QOL-AD	31	-	Dementia	12
9	Kim 2017	RCT	Body and mind	Occupation-centered activity program+meditation	Meditation	KQOL-AD	15	15	Dementia	12
10	Jeong 2019	RCT	Body and mind	Exercise+cognitive intervention program	None	SF-36	8	8	MCI	12
11	Siu 2020	Non-RCT	Body and mind	Tai Chi intervention	Social center program (calligraphy, handicrafts, old song singing class)	SF-12	80	80	MCI	16
12	Chang 2006	RCT	Mind	Group reminiscence therapy	None	GQOL-D	10	14	Dementia	8
13	Chung 2009	Pre/post	Mind	Intergenerational reminiscence program	-	QOL-AD	166	-	Dementia	12
14	Gu 2011	Pre/post	Mind	Group art therapy	-	LSI-A[3)]	10	-	Dementia	15
15	Waldorff 2012††	RCT	Mind	Psychosocial supportive intervention	Usual care	EQ-VAS (proxy rated)[4)]	167	163	AD	52
16	Søgaard 2013††	RCT	Mind	Psychosocial supportive intervention	Usual care	QALY	167	163	AD	3 years
17	Hong 2013	Pre/post	Mind	Forest healing program.	-	WHOQOL-BREF	15	-	MCI	3 days
18	Orrell 2014††	RCT	Mind	Maintenance CST	Usual care	QoL-AD, DEMQOL	123	113	Dementia	52
19	D'Amico 2015††	RCT	Mind	Maintenance CST	Usual care	ICER	123	113	Dementia	7
20	Kang 2016	RCT	Mind	Occupational therapy+computerized cognitive therapy	Occupational therapy	GQOL-D	15	15	Dementia	6
21	Park 2017	RCT	Mind	Electroencephalogram based self-cognition training+donepezil	Donepezil	EQ-5D	14	11	AD+VaD	8
22	Xu 2017	RCT	Mind	Creative storytelling project+piracetam	Piracetam	WHOQOL-BREF	36	36	MCI	16
23	Han 2020	RCT	Mind	Song-based CST	None	QOL-AD	12	12	MCI	10
24	Chen 2020	Non-RCT	Mind	Traditional opera intervention+routine nursing care	Routine nursing care	QOL-AD	21	22	dementia	12
25	Park 2020	Non-RCT	Mind	RERMA[5)] based music activity	None	QoL-AD	38	42	Mild dementia	16

Table 1. Continued 1

No	First author, year	Study design	Intervention category	Intervention		Outcome measure	Sample size		Patients	Treatment and follow-up duration (weeks)
				Treatment (TRT)	Comparison (CPR)		TRT	CPR		
26	Choi 2021	Non-RCT	Mind	Self-management program	-	GQOL-D	29	-	MCI	8
27	Cho 2010	RCT	Body	Physical therapy+combined exercise	Physical therapy	GQOL-D	15	15	VaD	12
28	Jung 2013	Pre/post	Body	Customized Exercise Program	-	QOL-AD	8	-	Dementia	12
29	Pitkala 2013	RCT	Body	Home-based exercise (home); Group-based exercise (adult rehabilitation daycare center)	Community care	cost	68; 61	65	AD	52
30	Lowery 2013††	RCT	Body	Physical exercise	Usual care	DEMQOL-proxy	57	59	Dementia	12
31	D'Amico 2016††	RCT	Body	Physical exercise	Usual care	ICER	57	59	Dementia	12
32	Lee 2016	RCT	Body	Cognitive rehabilitation program+video game (Wii)	Cognitive rehabilitation program	KQOL-AD	15	15	AD+MCI	12
33	Wang 2020	Non-RCT	Body	Chinese square dancing	None	SF-12	33	33	MCI	12
34	Chang 2021	RCT	Body	Chinese square dance exercise program	Normal life group	SF-12	62	62	MCI	18
35	Wang 2010	RCT	Nursing	Community nursing	Routine home care	SF-36	40	40	Senile dementia	52
36	Guan 2016	RCT	Nursing	Integration nursing	Conventional nursing	QOL-AD	36	36	AD	24
37	Zhou 2016	RCT	Nursing	Syndrome-differentiated nursing care	Routine nursing care	WHOQOL-100	53	53	Dementia	24
38	Li 2012	RCT	Acupuncture	Scalp acupuncture	Medication	SF-36	40	40	VaD	2
39	Shi 2012	Pre/post	Acupuncture	Acupuncture	-	DEMQOL	16	-	VaD	6
40	Kim 2021	RCT	Acupuncture	Hominis placenta pharmacopuncture	Placebo group (saline)	EQ-5D EQ-VAS GQOL-D ICER	15	15	MCI	8
41	Wang 2012	Retrospective cohort	Chinese or oriental medicine	Traditional Chinese medicine	-	CIQOL, ICER	1301	-	MCI	-
42	Kim 2013	Pre/post	Chinese or oriental medicine	Korean oriental medicine	-	GQOL-D	24	-	MCI	6
43	Zheng 2016	RCT	Acupuncture and mind	Acupuncture+invigorating Qi	Conventional western medicine	Morris dementia scale	40	40	Senile dementia	4

AD: Alzheimer's Disease, ADL: Activity of Daily Living, CIQOL: Cognitive-impairment quality of life, CST: cognitive stimulation therapy, DEMQOL: Dementia Quality of Life Questionnaire, GQOL-D: Geriatric Quality of Life-Dementia, HK: Hong Kong, LSI-A: Life Satisfaction Index-A, MCI: Mild Cognitive Impairment, Pre/Post: Pre- and Post-Intervention, PWI-ID: Personal Well-Being Index for Intellectually Disabled, QOL-AD: Alzheimer's Disease Quality of Life, RCT: Randomized controlled trials, SF-36: 36-items short-form health survey, VaD: Vascular Disease, WHOQOL-BREF: Brief Form of the World Health Organization Quality of Life, NOTE: [1]MINDVital is a multi-disciplinary rehabilitation program; [2]15D, 15-dimensional, standardized, self-administered measure of health-related quality of life; [3]LSI-A, The Life Satisfaction Index-A [4]EQ-VAS proxy rated, European quality of life visual analogue scale proxy rated, The caregiver completed the Danish validated version of EQ-5D-VAS, rating their impression of the patient's health-related quality of life, [5]PERMA; Positive emotion, Engagement, Meaning, Relationship, Accomplishment, †† 15, 16/ 18,19/ 30,31 literatures are based on the same RCT.

unclear. Of the studies, 52.0% (n=13) reported a lack of blinding of the study participants, and 56.0% (n=14) of the studies were unclear regarding the blinding of the outcome assessment.

The quality of the 18 non-RCTs included in this study's systematic analysis was evaluated using the

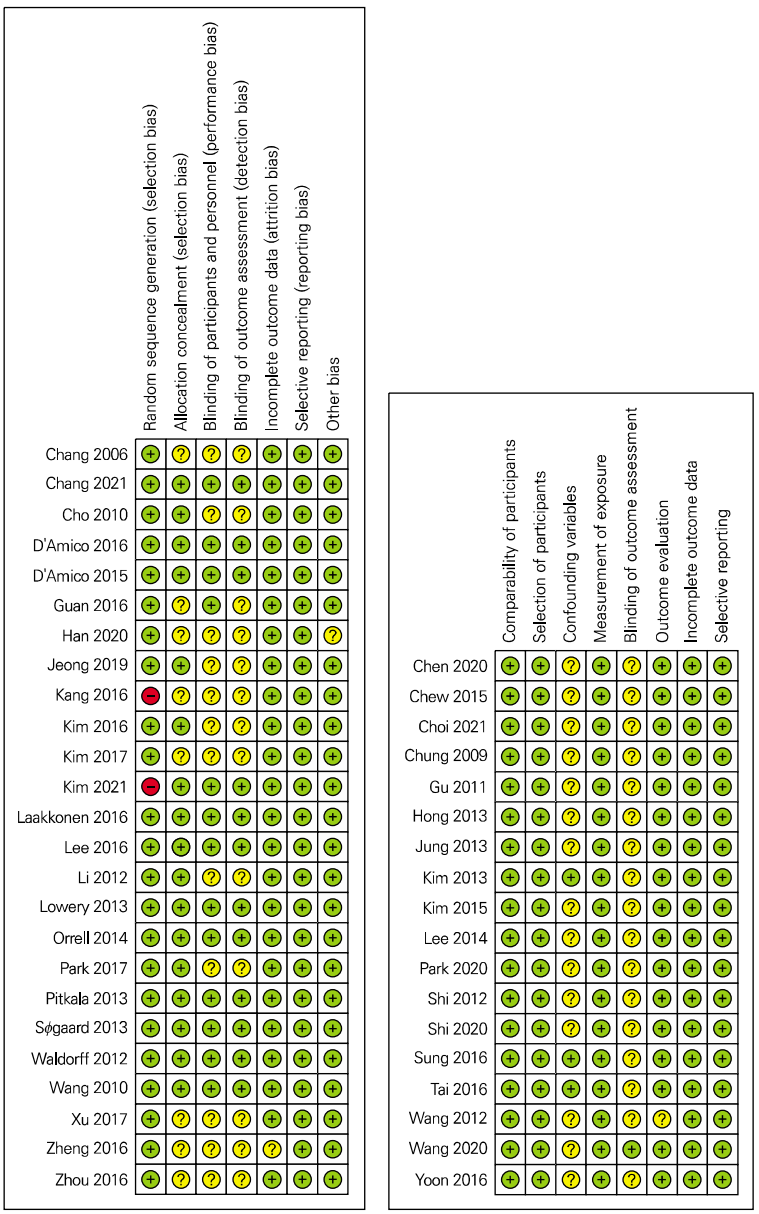

Fig. 2. Assessing the risk of bias in the randomized trials (left) and non-randomized studies of interventions (right).

RoBANS tool and is summarized in Fig. 2. All the studies were low risk in comparability, participant selection, incomplete outcome data, and selective reporting. All the non-RCT studies, except for one study[52], had an "unclear risk" in the blinding of the outcome assessment. This implied that we could not determine who assessed the outcomes.

3. Intervention effects

1) Meta-analysis of QoL outcomes

QoL outcomes were quantitatively measured in 25 studies. These estimates were combined through a meta-analysis to examine the integrated perform-

ance of CAM interventions for dementia. A meta-analysis was modeled for each of the four QoL instruments: 1) QOL-AD (n=10)[48,50,57,60,61,63,66,75,78,85]; 2) GQOL-D (n=7)[49,53,54,59,79,80,83]; 3) EQ-5D (n=2)[49,67] 4) SF-12 (n=3)[45,51,52] 5) SF-36 (n=2)[58,64]; and 6) WHOQOL-BREF (n=2)[72,84]. Kim's (2021) study was counted twice: EQ-5D and GQOL-D[49]. Although some studies reported the above-mentioned QoL outcomes, they were not included in the meta-analysis, due to the modified scales[46,47,71,74,77,81,86].

(1) QoL outcomes with QoL-AD instrument

The combined effect of the CAM based on the 10 studies investigated the single or add-on interventions of the body plus the mind[60,61,85], mind[48,50,66,75], body[63,78], and nursing programs[57], which indicated the QOL-AD estimates. The QoL-AD outcomes of the intervention group were higher than those of the active control group (SMD: 0.822; 95% CI, -0.087~1.732; p=0.08) (Fig. 3A). The CAM intervention within one group significantly increased the QoL-AD (SMD: 0.507; 95% CI, 0.191~0.824; p<0.01) (Fig. 3B). With the QoL-AD measurement between the two groups, the integrated nursing program[57] showed the largest increase. This was followed by the occupation-centered activity program[61]. Among the pre- or post-studies within one group, the Positive Emotion, Engagement, Meaning, Relationship, Accomplishment (PERMA)-based music therapy showed the largest increase[50].

(2) QoL outcomes with the GQOL-D instrument

The overall synthesized estimates evaluated with the GQOL-D showed significantly improved QoL in

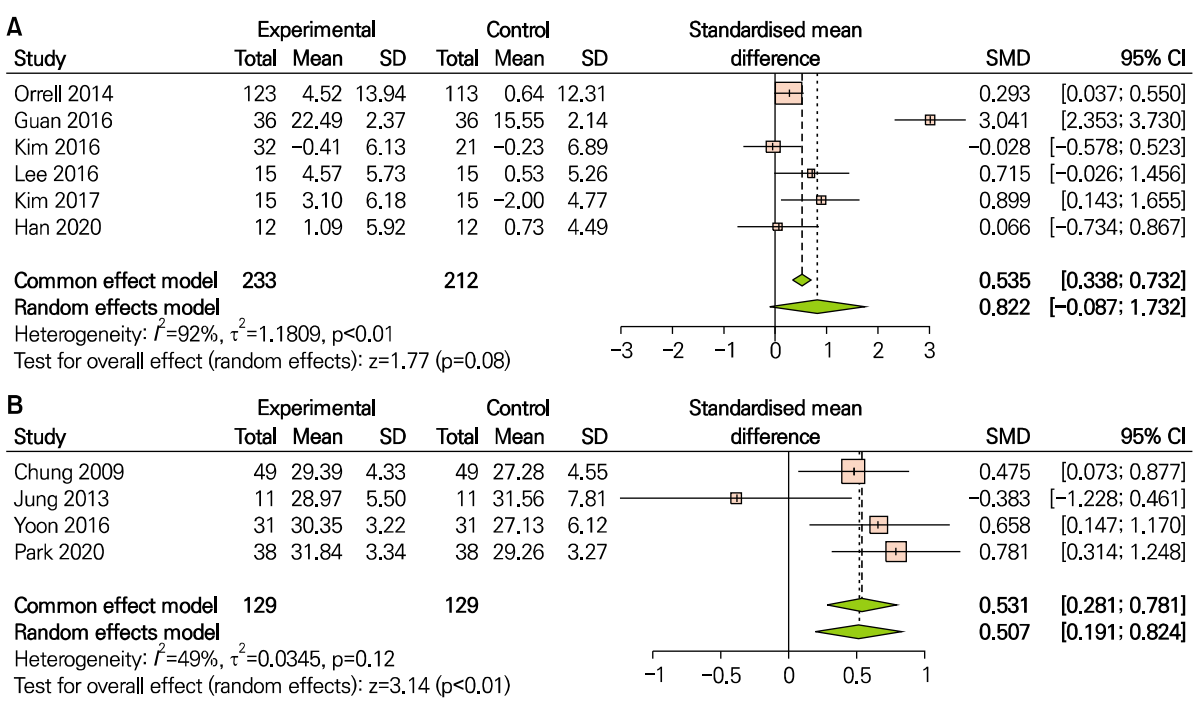

Fig. 3. (A). Meta-analysis of QoL-AD (two-group studies) QoL outcomes of the CAM interventions. Comparison of above studies were as follow: Maintenance CST vs Usual care (Orrell 2014), Integration nursing vs Conventional nursing (Guan 2016), Pharmacological Treatment & Cognitive and exercise program vs Pharmacological Treatment (Kim 2016), Cognitive rehabilitation program+video game (Wii) vs Cognitive Rehabilitation Program (Lee 2016), Occupation-centered activity program+Meditation vs Meditation (Kim 2017), Song-based CST vs None (Han 2020). (B) Meta-analysis of QoL-AD (one group study) QoL outcomes of the CAM intervention. Intervention of above studies were as follow: Intergenerational reminiscence program (Chung 2009), Customized Exercise Program (Jung 2013), Cognitive and physical activity Occupational therapy program (Yoon 2016), RERMA6) based music activity (Park 2020).

studies implementing two groups (SMD: 0.537, 95% CI: 0.238-0.837 $p<0.01$) (Fig. 4A) and one group (SMD: 1.465, 95% CI: 0.934-1.996 $p<0.01$) (Fig. 4B). Five studies evaluated the GQOL-D values for the interventions of the mind[53,59], body and mind[83], body[54], and acupuncture[49], as compared to the control group. The comparison groups were active control groups for physical therapy[54] and occupational therapy[59]. Group reminiscence therapy[53] showed the greatest improvement in QoL as measured via the GQOL-D. The CAM intervention in the pre- and post-study included two Korean oriental medicines, Jodeung-san (JDS) and Dangguijagyag-san (DGJYS)[80], and experience-based group therapy[79]. The difference before and after was the largest in JDS[80].

(3) QoL measured with EQ-5D

The combined effect of the two[49,67] studies showed that the EQ-5D estimates was negative (Fig. 5). Self-

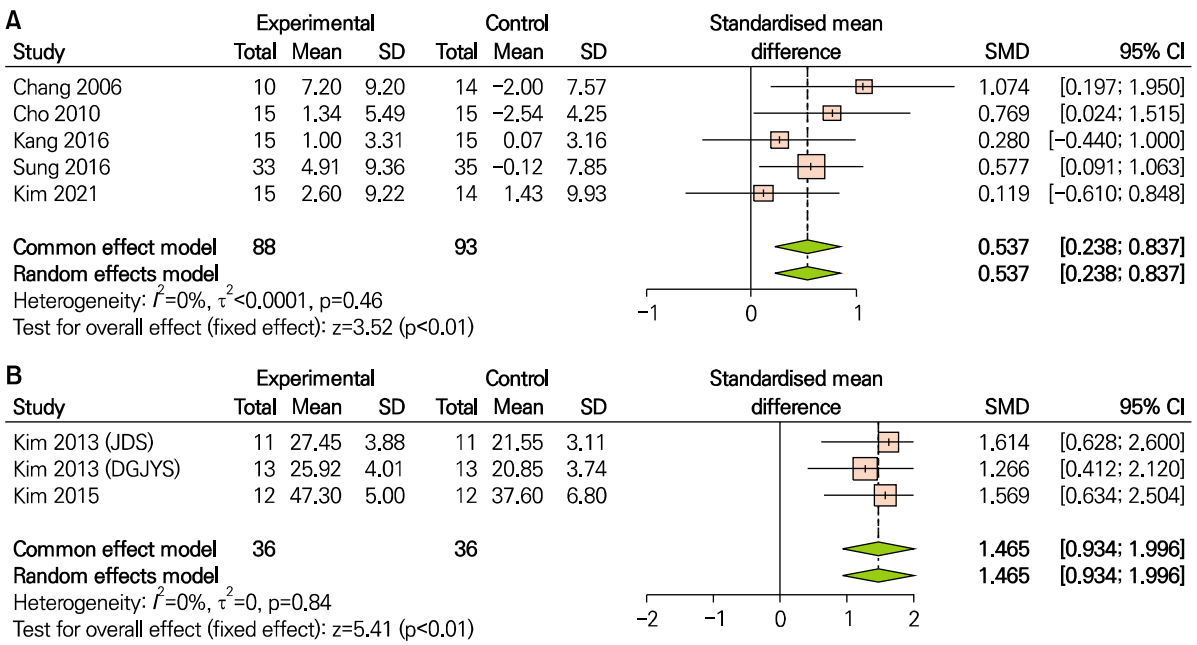

Fig. 4. (A) Meta-analysis of GQOL-D (two-group studies) QoL outcomes of the CAM interventions. Comparison of above studies were as follow: Group reminiscence therapy vs None (Chang 2006), Physical therapy+combined exercise vs Physical therapy (Cho 2010), Occupational therapy+computerized cognitive therapy vs Occupational therapy (Kang, 2016), Communication, Music, Art Therapy, Physical Exercise vs None (Sung 2016), Hominis placenta pharmacopuncture vs Placebo (saline) (Kim 2021). (B) Meta-analysis of GQOL-D (one group study) QoL outcomes of the CAM interventions. Intervention of above studies were as follow: Korean oriental medicine; Jodeung-san(JDS), Dangguijagyag-san(DGJYS) (Kim 2013), Experience-based group therapy (Kim 2015).

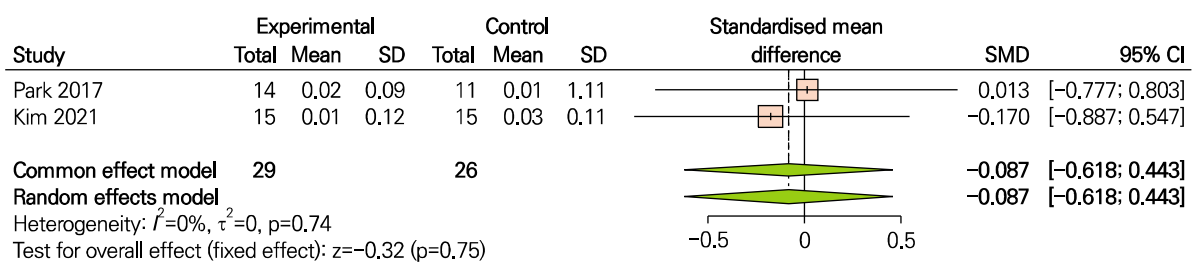

Fig. 5. Meta-analysis on the EQ-5D (two group studies) QoL outcomes of the CAM intervention. Comparison of above studies were as follow: Electroencephalogram based self-cognition training+Donepezil vs Donepezil (Park 2017), Hominis placenta pharmacopuncture vs Placebo (saline) (Kim 2021).

cognition training plus donepezil was effective in increasing QoL, as compared with donepezil alone[67]. However, pharmacopuncture did not demonstrate a positive outcome in the EQ-5D[49].

(4) QoL measured with SF-12

Three studies measured SF-12 and showed a significant increase in the (PCS SMD: 0.421, 95% CI: 0.184~0.659, p<0.01) and the mental component score (MCS SMD: 0.616, 95% CI: 0.258~0.975, p<0.01) (Fig. 6). The above CAM interventions included the body intervention of Chinese square dancing[45,52] and the body plus mind intervention of the Tai Chi program[51]. These interventions are mostly body interventions and they increased the MCS as compared to the PCS.

(5) QoL outcomes with SF-36 instrument

Two studies with SF-36 outcomes of the body plus mind for MCI (cognitive and exercise intervention program)[58] and acupuncture versus meditation for VaD[64] were synthesized (Fig. 7). There was no statistically significant difference in QoL improvement for the eight domains of the SF-36.

(6) QoL measured with WHOQOL-BREF

Three studies used the WHOQOL-BREF scale to examine the CAM interventions' effect. This included multiple training modalities in body plus mind therapy versus routine activity[84] and storytelling project (mind therapy) plus piracetam versus piracetam[72]. The synthesized results showed that the CAM interventions for treatment groups significantly improved two subdomains of WHOQOL-BREF: psychological (D2; SMD: 0.698, 95% CI, 0.284~1.113, p=0.001) and social relationship (D3; SMD: 0.569, 95% CI, 0.159~0.979 p=0.006) domains (Fig. 8).

2) Cost-effectiveness of the outcomes of the CAM interventions

Seven studies evaluated the cost-effectiveness of the CAM interventions. The interventions included the mind[55,69], body[56,68], body plus mind[62], acu-

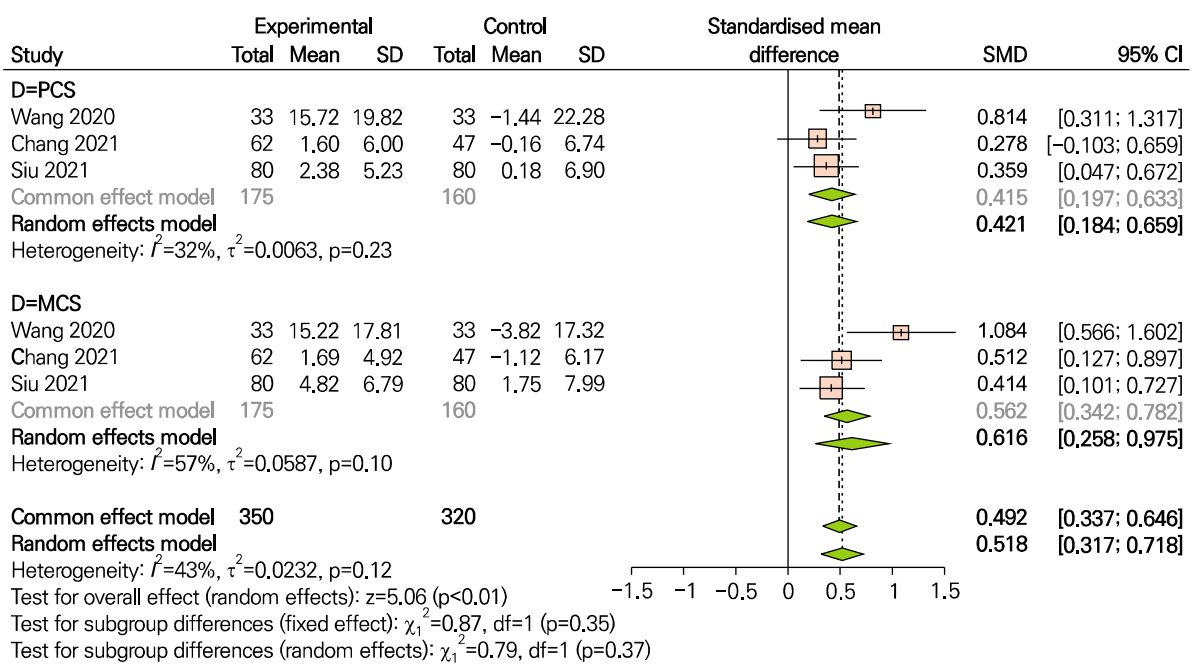

Fig. 6. Meta-analysis on SF-12 (two group studies) QoL outcomes of CAM intervention. Comparison of above studies were as follow: Chinese square dancing vs None (Wang 2020), Chinese square dance exercise program vs Normal life (Chang 2021), Tai Chi intervention vs Social center program (Siu 2021).

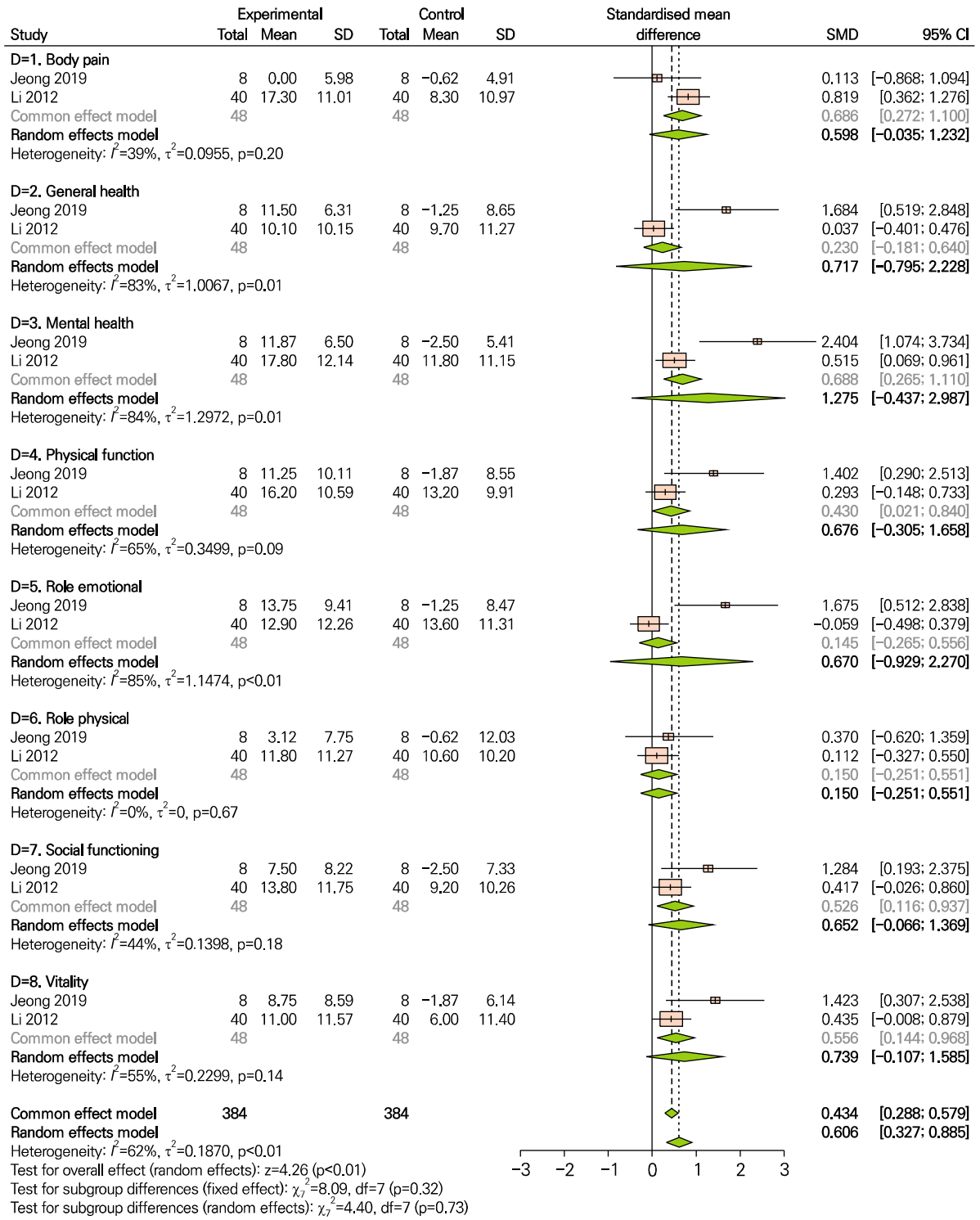

Fig. 7. Meta-analysis of SF-36 QoL outcomes of CAM interventions. Comparison of above studies were as follow: Exercise+Cognitive intervention program vs None (Jeong 2019), Scalp acupuncture vs Medication (Li 2012).

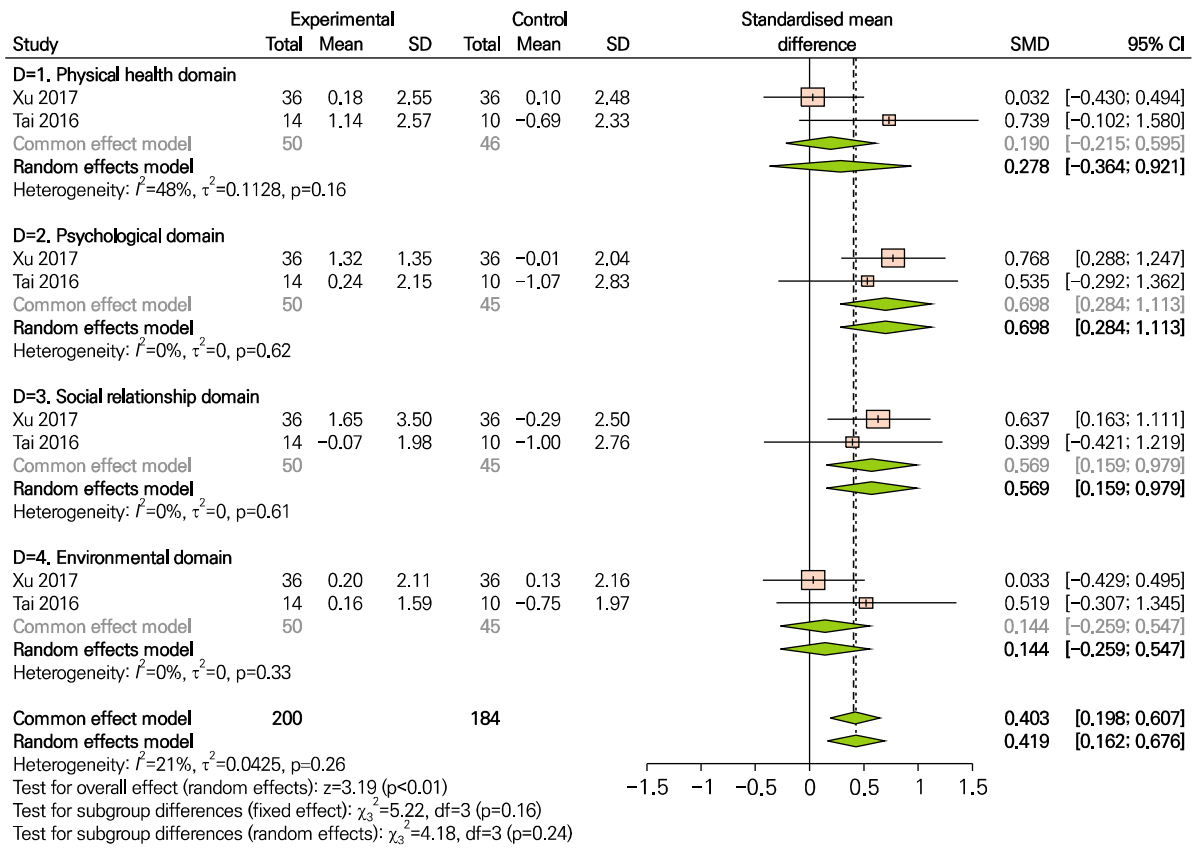

Fig. 8. Meta-analysis of the WHOQOL-Bref QoL outcomes after the CAM intervention. Comparison of above studies were as follow: Creative storytelling Project+Piracetam vs Piracetam (Xu 2017), Multiple training modalities (Tai Chi, Calligraphy, Drawing) vs Routine activity (Tai 2016).

puncture[49] and oriental medicine[87]. The cost-effectiveness of the mind intervention was somewhat unclear. Maintaining cognitive stimulation therapy (CST) for seven weeks generated 266 ICER (Euro per one unit of QOL-AD, in 2011), which was likely to be cost-effective in the UK[55]. Another model conducted in Denmark found no significant difference in the costs and EQ-VAS between a psychological intervention and the usual care[69]. Regarding the body intervention of the exercise, its ICER was €286,440 per QALY based on the DEMQOL-proxy in 2011. This exceeded the upper threshold of the €30,000 in the UK[56]. Another body intervention study examined only cost outcomes and reported that a group-based exercise was a cost-saving intervention ($22,066), as compared to tailored home-based exercise ($25,112) and a control group ($34,121) in 2012 in Finland[68]. In a cohort study of eight-session rehabilitation (body and mind intervention), there were no differences in the mental component of the RAND-36. Cost was neutral, as compared to the usual care group in Finland[62]. Oriental medicine yielded an ICER of 39,995 yuan/QALY (approximately $5,706 in 2021) in China in 2012[87]. A recent Korean pharmacopuncture study showed that the costs of hominis placenta pharmacopuncture treatment was 345,000 KRW more than that of the placebo group to increase the GQOL-D score by one point per year[49].

3) Systematic Review for each CAM intervention

(1) Mind treatment

Mind therapies, such as psychological support and

CST have shown positive results, as compared with the usual care control groups. The reminiscence therapies for seven to 12 weeks were useful for dementia patients[53,66,75] and was also reported as cost-effective (ICER=266 euro/QoL-AD)[55]. Psychological intervention, which was individually tailored to each dyad of the patient and primary caregiver for one year improved the EQ-VAS of the AD[70], although it was not statistically significant. Computerized cognitive therapy combined with occupational therapy improved GQOL-D[59]. Additional electroencephalogram-based self-cognitive training (EEG-based SCT)[67] and creative storytelling combination therapy[72] generated EQ-5D and WHOQOL-Bref increases, as compared to conventional pharmacotherapy. The self-management program also increased the GQOL-D in patients[47]. In addition, sense treatment, which involved group art therapy, significantly increased the QoL of dementia patients, as measured by the LSI-A scale (from 6.5 ± 2.5 to 11.5 ± 9.3, $p<0.05$)[76]. Music-based intervention, such as song-based CST, opera, and PERMA-based music activity, improved the QoL of dementia patients[46,48,50].

(2) Body

As physical exercise is encouraged to increase physical activity and improve QoL in patients with dementia, eight studies evaluated the QoL outcomes for five different types of body therapy interventions. Aerobic training and resistance exercise[54], virtual reality video game (Wii)[63], and tailored exercise programs[78] had a positive influence on the QoL of dementia patients as compared to the 30 min mattress activity or cognitive rehabilitation program. On the other hand, a three month exercise regimen tailored to a walking program did not appear to improve the DEMQOL-proxy of dementia, as compared to their usual care[65]. It was also not regarded as a cost-effective option in the UK[56]. In another cost analysis model, group-based exercise was determined as a cost-saving intervention, as compared to the tailored home-based exercise and control group in Finland[68]. Recent studies on Chinese square-dancing programs indicated that they were more effective for mental components than for physical components in the SF-36[45,52].

(3) Combination treatment of body and mind

Significant benefits were observed with increasing GQOL-D, QOL-AD, EQ-5D, and SF-36 scores for body intervention (exercise, occupational therapy, physical activity) plus mind intervention (cognitive intervention, meditation) for eight to 24 weeks[58,60,61,81,85]. In a few studies, more integrated interventions were provided by including music art, Tai Chi, or cooking activities, in addition to body and mind interventions. The participants showed an improvement in the GQOL-D, WHOQOL-Bref, and SF-12 measures[51,79,83,84]. In addition, a three-day forest healing program increased the WHOQOL-Bref of MCI[77]. However, rehabilitation programs, which aim to decrease functional disability and maximize social participation, did not appear to bring about a significant increase in EQ-5D in a cohort (Singapore)[86] or 15D in an RCT (Finland)[62].

(4) Nursing

Community nursing, integration nursing, and syndrome-differentiated care were reported to improve QoL, as measured by the SF-36, QOL-AD, and WHOQOL-100, respectively. This was in comparison with routine nursing care[57,71,74]. Wang (2010) and Guan (2016) showed that community care, including health knowledge education[57,71], psychological emotional support, and rehabilitation training, increased the QoL of dementia patients. This was in comparison to routine home care. Zhou (2016) studied the QoL effect of syndrome-differentiated nursing care coupled with memory training in patients with dementia[74].

(5) Oriental medicine

Two studies evaluated the QoL outcomes in oriental medicine[80,87]. Chinese medicine resulted in an ICER of 39,995 yuan/QALY (currently approximately $5,706) in 2012 in China. It is regarded as being cost-effective[87]. Regarding Korean medicines, JDS and DGJYS showed a significant increase (JDS; 1.614, DGJYS; 1.266) in the GQOL-D for patients with cognitive impairment (MCI) after six weeks of taking the herbal decoction[80].

(6) Acupuncture

Three studies demonstrated improvements in SF-36[64] and DEMQOL[82] for VaD after acupuncture treatment for two or six weeks and GQOL-D for MCI after pharmacopuncture for eight weeks. Another RCT conducted in China showed that acupuncture plus Qi was superior and effective by having significantly higher PLQI score changes (69.80±22.01 to 90.10±15.28) in the self-esteem domain over the traditional pharmacotherapy regimen that are commonly used (69.33±21.28 to 77.39±15.71). This was considered to be an effective option[73].

IV. DISCUSSION

This SR was conducted to evaluate the QoL and cost-effectiveness of CAM therapies in patients with dementia. A total of 43 articles in the English, Chinese, and Korean languages published until December 2021 were selected from several databases. They were reviewed, and meta-analyzed. Among these papers, the most frequently evaluated intervention was mind therapy (n=15, 34.9%), followed by body plus mind (n=11, 25.6%), body (n=8, 18.6%), nursing (n=3, 7.0%), acupuncture (n=3, 7.0%), Chinese or Oriental medicine (n=2, 4.7%), and acupuncture plus mind (n=1). Among them, approximately 90.7% (n=39) reported significantly improved QoL of CAM for dementia patients, except for four studies.

The most frequently used QoL measurement tools for the meta-analysis were QoL-AD and GQOL-D. The combined effect of CAM based on four studies (one group) showed that the QOL-AD estimates significantly increased as compared with the active control group (SMD: 0.507; 95% CI, 0.191-0.824; p=0.01). The overall synthesized estimates evaluated with the GQOL-D (two group studies) also showed significantly improved QoL (SMD: 0.537, 95% CI: 0.238-0.837 p=0.000). Based on seven studies evaluating CAM interventions' cost-effectiveness outcomes, it is difficult to state that mind or body interventions are more cost-effective. However, these therapies must have been alternative options as compared with several other CAM or conventional treatments.

CAM is the oldest form of global treatment that has been developed by different countries to address a diaspora of diseases[90]. While various pharmacological and non-pharmacological therapies are used to treat dementia and improve QoL, there is a long history of CAM implementation to boost memory and cognitive function. This includes managing the behavioral and psychological symptoms associated with dementia[91].

The study's results suggest that oriental medicines are effective in improving QoL and are cost-effective. Previous clinical studies indicated that oriental medicine may improve clinical outcomes regarding mini-mental status examination (MMSE) scores for dementia patients[92,93]. These include the Acorus calamus, Popygonum nultiflorum, and polygala root. In Korea, DGYS has often been used to treat patients with cognitive disorders, including MCI[94] and to increase the MMSE score for MCI[95]. Previous research on traditional Chinese and Japanese herbal medicine (TCM) mixtures also showed an improvement in scopolamine-induced memory impairment in mild and

severe dementia patients and rats[96,97]. Therefore, it may be inferred that those Oriental medicines improved the clinical symptoms and QoL of patients with dementia.

Although the treatment mechanism of acupuncture for VaD is not fully understood, the clinical effects of acupuncture on VaD have been reported in many clinical studies regarding one's activities of daily living (ADL) and MMSE[98-101]. Our study found that acupuncture was also effective in increasing QoL in VaD or senile dementia[64,73,82]. Although scientific evidence regarding the mechanism of acupuncture has only been found in animal studies[102], it has been suggested that acupuncture may be useful in relieving VaD symptoms and improving one's cerebral blood supply[103]. In addition to VaD patients, during acupuncture, AD and MCI patients showed activation in the temporal and frontal lobes, which are closely related to memory and cognition[104]. As these clinical symptoms improve, the QoL of dementia patients also improves.

Mind or body interventions are frequently used in patients with mental illnesses and cognitive disorders[105,106]. These approaches offer a more accessible and acceptable conventional mental health treatment for patients who may not otherwise receive treatment or those on whom conventional treatment had little effect[107]. A previous SR study reported that a mind-body intervention for MCI reduced one's risk of falling, depression, stress, and dementia within one year[108]. Another SR on exercise intervention for AD showed that 30~120 min of exercise interventions had a positive effect on global cognitive function[44]. Moreover, an SR identified cognitive therapy as a well-established mind intervention that positively influences cognitive impairment in dementia patients, although the results are inconclusive[109]. As our SR focuses on the QoL's effects, we have shown that mind and/or body interventions have a positive effect on dementia patients. Mind interventions, such as cognitive therapy, storytelling, and reminiscence therapy improved QoL with various instruments. These included GQOL-D, QOL-AD, WHOQOL, DEMQOL, EQ-5D, and EQ-VAS.

Regarding cost-effectiveness outcomes, mind therapy with cognitive stimulation was related to be cost-effective, whereas body therapy was not[55,56]. Although body intervention, such as exercise, does not cure dementia, it may delay the onset or progression of dementia in older adults[110-112]. Periodic exercise ameliorates negative physical problems, such as falls and fractures[113] and has a positive association with MMSE scores[114]. Our study showed that body interventions[54,56,63,65,68,78], such as exercise, improved the QoL in dementia patients. These mind and/or body intervention studies also examined the sense intervention. This included art therapy and forest healing programs, which were examined in this SR[76,77]. They suggested that music therapy, aroma therapy, herbal tea therapy, and exercise helped dementia patients to improve their cognitive function and relieve emotion.

In this SR, the most frequently used QoL instruments were the GQOL-D and QOL-AD (20/43; 46.5%). The GQOL-D consists of 15 items assessing cognition, psychological well-being, behavior, and ADL[115]. It was developed by including only items pertaining to the QoL of patients with dementia in Korea[116]. The QoL-AD is a 13-item questionnaire designed to assess the QoL reported by both a patient and a caregiver. It explores the relationship between QoL and demographic characteristics, such as cognitive and functional status, depression, and engagement in pleasant activities[117]. In addition, high QoL-AD scores were explained by low levels of depressive symptoms, more independent functioning in ADL, and more years of education[117]. Owing to its usefulness, QOL-AD is globally utilized in research and

clinical practice involving dementia patients[115]. Conversely, as our SR determined, over half the studies utilized various QOL instruments rather than the GQOL-D and QOL-AD.

The WHOQOL-BREF, SF-12, SF-36, and EQ-5D are generic QoL measures. The WHOQOL-BREF is a useful tool for assessing patients with mild-to-moderate dementia. This is because it includes important dimensions commonly omitted from other dementia measures[118]. Conversely, the SF-12 or SF-36 may not be suitable for severe dementia because it may be difficult to detect subtle changes or deterioration in a clinically critical state. Therefore, generic instruments utilized for the general population may be used to find out the health status of participants with mild to moderate dementia[119]. For patients with severe dementia, caregivers completed the QoL scale, rating their impression of the patient's QoL[56,65,69,70] in our SR. Thus, EQ-5D and DEMQOL were measured in two versions: EQ-5D, EQ-5D proxy or DEMQOL, and DEMQOL proxies.

Although the SF-12, SF-36, EQ-5D, and WHOQOL are widely used methods for QoL measurement, these instruments measure the overall good condition or general health of an individual's physical, mental, and social abilities. It is necessary to comprehensively consider the social and psychological impacts from the perspective of QoL. The EQ-5D proxy or DEMQOL-proxy may be a solution to these challenges because caregivers represent their patients' QoL. The Morris dementia scale evaluates one's living ability, self-esteem, and emotional condition[73]. LSI-A, a social and psychological measure, has been used in the fields of geriatrics and gerontology[120]. The CIQOL was also designed to measure QoL in patients with cognitive impairment[87].

In this study, the QoL outcomes may not be synthesized into a single segment of evidence because they were measured by using diverse instruments. If there is a newly developed CAM treatment, it is expected to introduce potentially incremental QoL outcomes for dementia. Thus, it may be helpful to use only a few standard QoL instruments in many clinical studies to compare and identify the marginal effects. Therefore, further research is required to organize QoLs for optimal selection according to the type and severity of dementia and a variety of interventions.

Our study has some limitations: First, most studies in our SR had bias assessments. The existence of bias may threaten the validity of the results. Nevertheless, our SR included these publications in an attempt to integrate the QoL's effects reported therein for various CAM interventions.

Second, there may have been a file-drawer effect or publication bias in our meta-analysis. It may be challenging to locate all articles or data sources exclusively, especially for CAM interventions. In addition, our meta-analysis may have missed studies that measured QoL outcomes using specific instruments whose names may not have been identified or mentioned in the study, which leads to a difficulty in identifying those studies. We searched the literature published in English, Korean, or Chinese for practical reasons. This may have resulted in the loss of research data on CAM for dementia published in other languages.

Third, the small sample size of the studies included in our meta-analysis may have led to a sampling error bias. This may have influenced the effect size of the meta-analysis[121]. Among the 43 final articles included in the meta-analysis, 11 had fewer than 30 participants. Although the random effects model was applied for the meta-analysis, the sampling error biases may not have been fully accounted for.

Fourth, we synthesized the general effects of various CAM programs on QoL outcomes by merging the QoL values measured with an identical scale for various interventions. This may have resulted in stat-

istical heterogeneity problems. In addition, high heterogeneity may have resulted from the differences across studies regarding single or a combination of interventions, study populations, or disease duration and severity. These limitations may be solved as more evidence and comprehensive results are accumulated. Therefore, further studies investigating QoL outcomes are required to ensure sufficient participants, adequate study duration and follow-up periods, and improved quality research performance.

Considering that dementia is a disease with long-term conditions, long-term follow-up monitoring is required. As temporary improvement does not constitute the sufficient management of dementia, the long-term benefits of CAM interventions should be investigated to obtain clinically meaningful information. In addition, more cost-effectiveness studies should be conducted to verify whether the CAM's merits are of economic value. As dementia burdens not only patients, but also society, the value of CAM should be established from the payer's or societal perspectives.

V. CONCLUSION

This study indicated that CAM interventions assist patients with dementia by improving their QoL. Considering that dementia is a disease that degenerates one's QoL and aggravates the disease burden in patients and society, CAM therapies may be considered a part of the clinical management of dementia. They may be utilized to complement the most common pharmacological treatment. Furthermore, policymakers may need to consider expanding the coverage of health insurance to include CAM treatment for dementia patients to improve the QoL and societal benefits provided by CAM interventions.

AUTHOR CONTRIBUTIONS

Conceptualization: LSY, JIC, and JE. Methodology: LSY, JIC. Software: LSY. Validation: JE. Formal analysis: LSY, JE. Investigation: LSY, JE. Resources: LSY, JIC. Data curation: LSY, JIC. Writing – Original Draft: LSY, JIC. Writing – Review & Editing: JE. Visualization: LSY, JE. Supervision: JE. Project administration: JE. Funding acquisition: None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL STATEMENT

None.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. World Health Organization. Dementia. 2021. Available from: URL: https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed January 11, 2021.
2. The Alzheimer's Association. 2020 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2020;16: 391-460.
3. Lancet Neurology. Response to the growing dementia burden must be faster. Lancet Neurol. 2018;17: 651.
4. Ninomiya T, Kiyohara H, Ohara T. Research on future estimation of the elderly population with dementia in Japan future estimation of the number of dementia patients in Japan. The Ministry of Health, Labor and Welfare Grants. 2015:20-4.
5. Kim S, Lee C. Status and improvement tasks of dementia management plan. Seoul: National Assembly Budget Office. 2014.

6. Statistics Korea. Korea in terms of population. (2021). Available from: URL: https://kosis.kr/visual/populationKorea/PopulationByNumber/PopulationByNumberMain.do?mb=Y&menuId=M_1_4&themaId=D03 Accessed November 23, 2021.
7. Lee JS, Kang MJ, Nam HJ, et al. Korean dementia observatory 2019. In Central Dementia Cente; 2019: 34.
8. Karg N, Graessel E, Randzio O, Pendergrass A. Dementia as a predictor of care-related quality of life in informal caregivers: a cross-sectional study to investigate differences in health-related outcomes between dementia and non-dementia caregivers. BMC Ger. 2018; 18(1):189-9.
9. Ballard CG, O'Brien JT, Reichelt K, Perry EK. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. J. Cinic Psychia. 2002;63:1369.
10. Budson AE, Solomon PR. Memory loss, alzheimer's disease, and dementia. London: Elsevier; 2016.
11. Casey DA, Antimisiaris D, O'Brien J. Drugs for Alzheimer's disease: are they effective? PT. 2010; 35(4):208-11.
12. Possin KL, Merrilees JJ, Dulaney S, et al. Effect of collaborative dementia care via telephone and internet on quality of life, caregiver well-being, and health care use: the care ecosystem randomized clinical trial. JAMA Int Medic. 2019;179(12):1658-67.
13. Howe E. Improving the quality of life in patients with Alzheimer's disease. Psychiat. 2008;5(8):51-6.
14. National Center for Complementary and Inetgrative Health. Complementary, alternative, or integrative health: what's in a name? 2021. Available from: URL: https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name Accessed June 1, 2020.
15. Hamuro A, Isono H, Sugai Y, Mimura M, Kamijima K. Characteristics of behavioral and psychological symptoms of dementia in untreated oldest old Alzheimer's disease*. Psychogeriat. 2008;8(1):8-11.
16. Takeda M, Hashimoto R, Kudo T, et al. Laughter and humor as complementary and alternative medicines for dementia patients. BMC Complement Altern Med 2010; 10(1):28.
17. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochr Data System Revs. 2018; (6): 1465-858.
18. Dunn N, Pearce G, Shakir S. Adverse effects associated with the use of donepezil in general practice in England. J Psychopharma. 2000;14(4):406-8.
19. Landin J, Frölich L, Schwarz S. Use of alternative therapies in patients with dementia and mild cognitive impairment: a prospective, controlled study. Int J Geriatr Psychiatry. 2008;23(11):1163-5.
20. Shi J, Ni J, Lu T, et al. Adding Chinese herbal medicine to conventional therapy brings cognitive benefits to patients with Alzheimer's disease: a retrospective analysis. BMC Complement Altern Med. 2017;17(1):533-3.
21. Jia Y, Zhang X, Yu J, et al. Acupuncture for patients with mild to moderate Alzheimer's disease: a randomized controlled trial. BMC Complement Altern Med. 2017; 17(1):556.
22. Yancheva S, Ihl R, Nikolova G, et al. Ginkgo biloba extract EGb 761®, donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomised, double-blind, exploratory trial. Aging Ment Health. 2009;13(2):183-90.
23. Chapman SB, Weiner MF, Rackley A, Hynan LS, Zientz J. Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. J Speech, Lang, & Hear Res. 2004;47(5):1149-63.
24. Chapman SB, Weiner MF, Rackley A, Hynan LS, Zientz J. Effects of cognitive-communication stimulation for alzheimer's disease patients treated with donepezil. J Speech, Lang, & Hear Res 2004;47(5):1149.
25. Lavretsky H. Complementary and alternative medicine use for treatment and prevention of late-life mood and cognitive disorders. Aging Health. 2009;5(1):61-78.
26. Poulos CJ, Bayer A, Beaupre L, et al. A comprehensive approach to reablement in dementia. Alzh & Dem. 2017; 3(3):450-8.
27. Robotin M, Olver IN: Perspectives on complementary and alternative medicines. World scientific Publishing Company; 2011.
28. Verhoef MJ, Vanderheyden LC, Dryden T, Mallory D, Ware MA. Evaluating complementary and alternative medicine interventions: in search of appropriate patient-centered outcome measures. BMC Complement Altern Med. 2006;6:6-38.
29. Lafferty WE, Tyree PT, Bellas AS, et al. Insurance coverage and subsequent utilization of complementary and alternative medical (CAM) providers. Amer J Manag Care. 2006;12(7):397.
30. Joos S, Musselmann B, Miksch A, Rosemann T, Szecsenyi J. The role of complementary and alternative medicine (CAM) in Germany–a focus group study of GPs. BMC Health Serv Res 2008;8(1):1-13.
31. Sheehan B. Assessment scales in dementia. Ther Adv Neurol Disord. 2012;5(6):349-58.
32. Alarcos C, Stucki G. Content comparison of Health-Related Quality of Life (HRQOL) instruments based on the International Classification of Functioning, Disability and Health (ICF). Qual Life Res. 2005;14(5):1225-37.
33. Smith S, Lamping D, Banerjee S, et al. Development of a new measure of health-related quality of life for people with dementia: DEMQOL. J Psychol Medic. 2007;37(5): 737.
34. Thorgrimsen L, Selwood A, Spector A, et al. Whose quality of life is it anyway?: The validity and reliability of

the Quality of Life-Alzheimer's Disease (QoL-AD) scale. J Alzh Dis Assoc Disord. 2003;17(4):201-8.
35. Fung JKK, Tsang HW, Chung RC. A systematic review of the use of aromatherapy in treatment of behavioral problems in dementia. Geriatr & Geront Intern. 2012; 12(3):372-82.
36. Zeng L, Zou Y, Kong L, et al. Can Chinese herbal medicine adjunctive therapy improve outcomes of senile vascular dementia? Systematic review with meta-analysis of clinical trials. Phytother Res. 2015;29(12):1843-57.
37. McDermott O, Charlesworth G, Hogervorst E, et al. Psychosocial interventions for people with dementia: a synthesis of systematic reviews. Aging & Ment Health. 2019; 23(4):393-403.
38. Sun Y, Zhang X, Wang Z. Comparative effectiveness of 3 settings of cognitive stimulation therapy on cognition and quality of life for people with dementia: a systematic review and network. J Am Med Dir Assoc. 2021;23(3): 461-7.
39. Nickel F, Barth J, Kolominsky-Rabas PL. Health economic evaluations of non-pharmacological interventions for persons with dementia and their informal caregivers: a systematic review. BMC Ger. 2018;18(1):69.
40. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011; 343:d5928.
41. Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemio. 2013;66(4):408-14.
42. Olazarán J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dem & Geriat Cog Disord. 2010;30(2): 161-78.
43. Anderson AR, Deng J, Anthony RS, Atalla SA, Monroe TB. Using complementary and alternative medicine to treat pain and agitation in dementia: a review of randomized controlled trials from long-term care with potential use in critical care. Crit Care Nurs Clin North Am. 2017; 29(4):519-37.
44. Farina N, Rusted J, Tabet N. The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. Int Psychogeriatr. 2014;26(1):9-18.
45. Chang J, Zhu W, Zhang J, et al. The effect of chinese square dance exercise on cognitive function in older women with mild cognitive impairment: the mediating effect of mood status and quality of life. Front in Psychia. 2021;12:711079.
46. Chen X, Li D, Xu H, Hu Z. Effect of traditional opera on older adults with dementia. Geriat Nurs. 2020;41(2): 118-23.
47. Choi HS, Jang TY. Effect of self-management program on self-efficacy, quality of life, and depression in patients with mild cognitive impairment. J Occ Ther for Aged & Dem. 2021;15(1):23-9.
48. Han EY, Park JS, Kim HY, et al. Cognitive intervention with musical stimuli using digital devices on mild cognitive impairment: a pilot study. Healthc. 2020, 8(1):45.
49. Kim YN, Eom YJ, Kwon DH, et al. Effect of hominis placenta pharmacopuncture for a patient with mild cognitive impairment: a randomized, double-blind, placebo-controlled, multi-center trial. J of Oriental Neuropsychiatry. 2021;32(2):81-93.
50. Park EY, Hwang EY. Effects of PERMA-based music activity on depression, interpersonal relationships and quality of life in the elderly with mild dementia in long-term care facilities. J Arts Psychother. 2020;16(2):273-300.
51. Siu MY, Lee DTF. Is Tai Chi an effective intervention for enhancing health-related quality of life in older people with mild cognitive impairment? An interventional study. Intern Jour Older People Nurs. 2021;16(5):e12400.
52. Wang S, Yin H, Meng X, et al. Effects of Chinese square dancing on older adults with mild cognitive impairment. Geriat Nurs. 2020;41(3):290-6.
53. Chang WS, Lee JM. The effect of group reminiscence therapy on depression, quality of life and social behavior of patients with dementia. J Welf for Aged. 2006;34: 239-270.
54. Cho SH. The effect of combined exercise programs on cognitive function and quality of living in the vascular dementia elders. J Kor Soc Phy Med. 2010;5(4):633-44.
55. D'Amico F, Rehill A, Knapp M, et al. Maintenance cognitive stimulation therapy: an economic evaluation within a randomized controlled trial. J Amer Med Direct Associat. 2015;16(1):63-70.
56. D'Amico F, Rehill A, Knapp M, et al. Cost-effectiveness of exercise as a therapy for behavioural and psychological symptoms of dementia within the EVIDEM-E randomised controlled trial. Int J Geriatr Psychiatry. 2016;31(6):656-65.
57. Guan X, Nao J. Influence on integration nursing for the life quality and activity of daily living of patients with Alzheimer's disease. China Medical Herald. 2016;(20): 153-6.
58. Jeong MK, Jung HH, Park SK. Effects of exercise and cognitive intervention program on cognitive function, sedentary behavior and health-related quality of life in elderly women with mild cognitive impairment. Exer Sci. 2019;28(2):198-204.
59. Kang JH. Effect of computerized cognitive training on cognitive function, instrumental activities of daily living and quality of life in patients with mild dementia. J Kor Aging Friend Indus Associat. 2016;8(2):71-83.
60. Kim HJ, Yang YS, Oh JG, et al. Effectiveness of a community-based multidomain cognitive intervention program in patients with Alzheimer's disease. Geriatr & Geront Internat. 2016;16(2):191-9.
61. Kim KU, Kim SH, Oh HW. The effects of occupation-cen-

tered activity program on fall-related factors and quality of life in patients with dementia. J Phys Ther Sci. 2017; 29(7):1188-91.
62. Laakkonen ML, Kautiainen H, Holtta E, et al. Effects of self-management groups for people with dementia and their spouses--randomized controlled trial. J Am Geriatr Soc. 2016;64(4):752-60.
63. Lee GH. Effects of virtual reality exercise program on balance, emotion and quality of life in patients with cognitive decline. J Kor Phys Ther. 2016;28(6):355-63.
64. Li SK, Ding DM, Liu Q, et al. Randomized controlled study on scalp acupuncture for vascular dementia. Shanghai J Acu-mox. 2012;(11):806-8.
65. Lowery D, Cerga-Pashoja A, Iliffe S, et al. The effect of exercise on behavioural and psychological symptoms of dementia: the EVIDEM-E randomised controlled clinical trial. Int J Geriatr Psychiatry. 2014;29(8):819-27.
66. Orrell M, Aguirre E, Spector A, et al. Maintenance cognitive stimulation therapy for dementia: single-blind, multicentre, pragmatic randomised controlled trial. Brit J Psych. 2014;204(6):454-61.
67. Park MS, Min JH, Shin YI, Ko SH. Effects of combination therapy with donepezil and electroencephalogram based self-cognition training in dementia. J Occu Thera for Aged & Dem. 2017;11(2):1-9.
68. Pitkala KH, Poysti MM, Laakkonen ML, et al. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. JAMA Inter Med. 2013; 173(10):894-901.
69. Søgaard R, Sørensen J, Waldorff FB, et al. Early psychosocial intervention in Alzheimer's disease: cost utility evaluation alongside the Danish Alzheimer's Intervention Study (DAISY). BMJ Open. 2014;4(1):e004105-p.
70. Waldorff FB, Buss DV, Eckermann A, et al. Efficacy of psychosocial intervention in patients with mild Alzheimer's disease: the multicentre, rater blinded, randomised Danish Alzheimer Intervention Study (DAISY). BMJ: Brit Med J. 2012;345:e4693.
71. Wang Z, Mu JB, Liu R. Community nursing intervention on quality of life in patients with senile dementia. Mod Preven Med. 2010;37(5):840-4.
72. Xu L, Deng X, Zhang Z. Application of creative storytelling project for elderly patients with mild cognitive impairment. Chinese Nurs Res. 2017(02):197-200.
73. Zheng W, Zhang W. Effect of the C reactive protein, quality of life and clinical efficacy by invigorating qi and activating blood method combined with acupuncture in senile dementia patients. J Liaoning University of TCM. 2016;18(06):173-5.
74. Zhou Q, Ge Z. Syndrom-differentiated nursing care coupled with memory training for the elderly with dementia. J Nurs Sci. 2016;31(21):17-20.
75. Chung J. An intergenerational reminiscence programme for older adults with early dementia and youth volunteers: values and challenges. Scandin J Caring Sci. 2009; 23(2):259-64.
76. Gu JK. The effects of group art therapy through the reminiscence method on depression and quality of life for the elderly with dementia. J Kor Acad Clin Art Ther. 2011;6(2):92-9.
77. Hong SS, Kim HC, Cho SH. The effects of forests healing for cognitive function. J Orient Neuropsych. 2013; 24(1):63-74.
78. Jung DY, Yi KO, Kim HJ. The effects of exercise program for bed-ridden dementia elderly adults who resided in nursing home. J Kor Phys Edu Assoc Girls & Women. 2013;27(3):179-91.
79. Kim HH. Effects of experience-based group therapy on cognitive and physical functions and psychological symptoms of elderly people with mild dementia. J Phys Ther Sci. 2015;27(7):2069-71.
80. Kim KH, Lee SI. The effect of mild cognitive impairment management program on traditional Korean medicine in a public health center. J Kor Med. 2013;34(3):106-18.
81. Lee YJ, Lee JH, Kim YJ, Yang NY. The effect of multimodal intervention on quality of life, depression, and cognitive function in elderly people with dementia: a pilot study. J Kor Soc Occupat Ther. 2014;22(3):85-98.
82. Shi GX, Liu CZ, Li QQ. Influence of acupuncture on cognitive function and markers of oxidative DNA damage in patients with vascular dementia. J Trad Chinese Med. 2012;32(02):199-202.
83. Sung MR, Lee DY. Effects of community based group validation therapy on depression, quality of life, behavioral problems, and cognitive function in patients with dementia. J Kor Gerontol Nurs. 2016;18(1):22-31.
84. Tai SY, Hsu CL, Huang SW, et al. Effects of multiple training modalities in patients with Alzheimer's disease: a pilot study. Neuropsych Dis & Treatm. 2016; 12:2843-49.
85. Yoon HS, Lee KS, Jeong WM, Park YJ, Park HU. Effects of home-based cognitive and physico-occupational therapy program on cognitive function, depression and quality of life in dementia patients of a community. Kor J Health Educ Promot. 2016;33(1):23-31.
86. Chew J, Chong MS, Fong YL, Tay l. Outcomes of a multimodal cognitive and physical rehabilitation program for persons with mild dementia and their caregivers: a goal-oriented approach. Clin Intervent in Aging. 2015; 10:1687-94.
87. Wang N, Zhang ZJ, Chang D. Using Markov model to cost-effectiveness analysis of traditional Chinese medicine interference. China J Chinese Mater Medica. 2012; (18):2698-701.
88. Johns Hopkins Medicine. Types of complementary and alternative medicine. Available from:URL: https://www.hopkinsmedicine.org/health/wellness-and-prevention/types-of-complementary-and-alternative-medicine. Accessed November 24, 2019.

89. Sogaard R, Sorensen J, Waldorff FB, et al. Cost analysis of early psychosocial intervention in Alzheimer's disease. Dement Geriatr Cogn Disord. 2014;37(3-4):141-53.
90. Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016;21(5):559.
91. Chang D, Liu J, Bilinski K, et al. Herbal medicine for the treatment of vascular dementia: an overview of scientific evidence. Evid Comp Alt Med. 2016;2016:7293626.
92. Wang W, Diwu Y, Liu Q, et al. Chinese herbal medicine for mild cognitive impairment using mini-mental state examination: a systematic review and meta-analysis. Med 2021;100(38):e27034-e27034.
93. Zhang Y, Lin C, Zhang L, et al. Cognitive improvement during treatment for mild alzheimer's disease with a chinese herbal formula: a randomized controlled trial. PLOS One. 2015;10(6):e0130353.
94. Kim KH, Go HY, Lee JA, et al. The effect of Dangguijagyagsan on mild cognitive impairment. J Altern & Complem Med. 2016;22(7):509-14.
95. Kim YN, Bae JS, Eom YJ, et al. Results of Korean medicine treatment in community dwelling elderly with mild cognitive impairment: focusing on the change in cognitive ability. J of Orien Neuropsych. 2019;30(3):185-98.
96. Iwasaki K, Kobayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "ba wei di huang wan" in the treatment of dementia. J Amer Geriatr Soc. 2004;52(9): 1518-21.
97. Tong YC, Cheng JT, Wan WC. Effects of Ba-Wei-Die-Huang-Wan on the cholinergic function and protein expression of M2 muscarinic receptor of the urinary bladder in diabetic rats. Neurosci Let. 2002;330(1):21-4.
98. Yu J, Zhang X, Liu C, Meng Y, Han J. Effect of acupuncture treatment on vascular dementia. Neurol Res. 2006; 28(1):97-103.
99. Shi GX, Liu CZ, Guan W, et al. Effects of acupuncture on Chinese medicine syndromes of vascular dementia. Chinese J Integrat Medic. 2014;20(9):661-6.
100. Shi GX, Li QQ, Yang BF, et al. Acupuncture for vascular dementia: a pragmatic randomized clinical trial. Sci World J. 2015;2015:161439-p.
101. Tang Y, Shao S, Zhou Y, et al. The effects of acupuncture on cognitive impairment of vascular dementia patients: protocol for a systematic review and meta-analysis. Medicine. 2019;98(43): e17648.
102. Ye Y, Zhu W, Wang XR, et al. Mechanisms of acupuncture on vascular dementia-a review of animal studies. Neurochemist Internat. 2017;107:204-10.
103. Yu J, Zhang X, Liu C, Meng Y, Han J. Effect of acupuncture treatment on vascular dementia. Neurolog Res. 2006;28(1):97-103.
104. Wang Z, Nie B, Li D, et al. Effect of acupuncture in mild cognitive impairment and Alzheimer disease: a functional MRI study. PLoS One. 2012;7(8):e42730.
105. Vasudev A, Torres-Platas S, Kerfoot K, et al. Mind-body interventions in late-life mental illnesses and cognitive disorders: a narrative review. Amer J Ger Psychia. 2018; 27:536-47.
106. Bandealy SS, Sheth NC, Matuella SK, et al. Mind-body interventions for anxiety disorders: a review of the evidence base for mental health practitioners. Focus. 2021;19(2):173-83.
107. Burnett-Zeigler I, Schuette S, Victorson D, Wisner KL. Mind-body approaches to treating mental health symptoms among disadvantaged populations: a comprehensive review. J. Alter Compl Med. 2016;22(2):115-24.
108. Farhang M, Miranda-Castillo C, Rubio M, Furtado G. Impact of mind-body interventions in older adults with mild cognitive impairment: a systematic review. Intern Psychoger 2019;31(5):643-66.
109. Carrion C, Folkvord F, Anastasiadou D, Aymerich M. Cognitive therapy for dementia patients: a systematic review. Dem & Ger Cog Dis. 2018;46(1-2):1-26.
110. Abbott RD, White LR, Ross GW, et al. Walking and dementia in physically capable elderly men. JAMA. 2004;292(12):1447-53.
111. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med. 2006;144(2):73-81.
112. Andel R, Crowe M, Pedersen NL, et al. Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. J Gerontol A Biol Sci Med Sci. 2008;63(1):62-6.
113. Rolland Y, Pillard F, Klapouszczak A, et al. Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J Am Geriatr Soc. 2007;55(2):158-65.
114. Koh YS, Oh YS, Park HS, Kim WR, Park EC. The relationship between physical exercise and cognitive function in Korean middle aged and elderly adults without dementia. Int J Environ Res Public Health. 2020;17(23): 8821.
115. Lee HS, Kim JH, Ko HJ, et al. The standardization of the geriatric quality of life scale-dementia (GQOL-D). J Kor Ger Soc. 2004;8(3):151-64.
116. Park EY, Park SM, Kim JH. Psychometric properties of the geriatric quality of life-dementia in older adults with dementia or mild cognitive impairment living in nursing homes. BMC Ger. 2019;19(1):281.
117. Logsdon RG, Gibbons LE, McCurry SM, Teri L. Quality of life in Alzheimer's disease: patient and caregiver reports. J Ment Health & Aging. 1999;5(1):21-32.
118. Lucas-Carrasco R, Skevington SM, Gómez-Benito J, Rejas J, March J. Using the WHOQOL-BREF in persons with dementia: a validation study. Alzh Dis & Assoc Disor. 2011; 25(4):345-51.

119. Novella J, Jochum C, Ankri J, et al. Measuring general health status in dementia: practical and methodological issues in using the SF-36. Aging Clin & Exp Res. 2001; 13(5):362-9.
120. Elmståhl S, Berglund JS, Fagerström C, Ekström H. The Life Satisfaction Index-A (LSI-A): normative data for a general Swedish population aged 60 to 93 years. Clinic Interv Aging. 2020;15:2031.
121. Lin L. Bias caused by sampling error in meta-analysis with small sample sizes. PLoS One. 2018;13:(9):e0204056.