Original Article

A systematic review and meta-analysis of the clinical effects of Souvenaid in patients with Alzheimer's disease

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Background and Objectives: We conducted this meta-analysis about the effects of Souvenaid on cognition and functional abilities, with the hypothesis that Souvenaid may have beneficial effects in certain groups and the goal of finding the outcome measures, disease states, and so on, applicable for further clinical trials. **Methods and Study Design:** We searched Medline, Embase, Web of Science, CINAHL, and the Cochrane Library. Only double-blind randomized controlled trials were included. Outcome measurements were cognition, clinical global change, functional ability, and adverse events. The duration of treatment was not restricted, but trials performed in patients who did not have Alzheimer's disease (AD) were excluded. **Results:** This review using meta-analyses of 4 clinical trials showed that Souvenaid had no significant effects on cognition as measured by ADAS-Cog (MD=0.08, 95% CI=−0.71-0.88) and the neuropsychological test battery total scores (MD=0.05, 95% CI=-0,02-0.12), on global clinical function as measured by CDR-SB (MD=-0.21, 95% CI=−0.47-0.06), or on functional ability as measured by ADCS-ADL (MD=0.36, 95% CI=−0.54-1.25). There were no differences in any adverse events (OR=0.84, 95% CI=0.63-1.12) or in serious adverse events (OR=0.95, 95% CI=0.66-1.36). However, Souvenaid may benefit the domains of cognition that are affected by AD (attention, memory, and executive function), and it may have greater potential for benefits earlier rather than later in the disease. **Conclusions:** The results of current clinical trials do not suggest that Souvenaid has any beneficial effects on cognition, functional ability, or global clinical change. Further studies with outcome measures suitable in patients with early stages of AD will be needed.

Key Words: Alzheimer's disease, Souvenaid, cognition, clinical trial, meta-analysis

INTRODUCTION

Alzheimer's disease (AD), which is the most common disease causing dementia, is clinically characterized by an irreversible, progressive cognitive decline and accompanied by functional deficits including difficulties in activities of daily living.[1] Although the amyloid hypothesis is prevailing in AD, complex interactions of various factors are important in AD pathophysiology.[2,3] Some drugs are currently used for symptomatic treatment, but there is no disease-modifying therapy for patients with AD to date. Also, for patients with mild cognitive impairment (MCI), there are no therapies preventing the progression into AD. Therefore, there have been many concerns about the non-pharmacological management, which suggested that nutrition can reduce the risk of AD and delay its progression.[4] Some observational studies have suggested that specific diets may have protective effects with respect to AD development; however, clinical trials for AD or cognitive decline have not yet shown consistent or conclusive results.[5-7]

Among many nutritional components, Souvenaid is considered to be able to have beneficial effects in AD.[8,9] Fortasyn Connect, the active component of Souvenaid, is a multi-nutrient combination consisting of omega-3 fatty acids; a vitamin B complex including pyridoxine, cyanocobalamin, and folate; vitamin E; choline; phospholipids; and selenium, among others.[10] Previous studies showed that Souvenaid improved cerebral metabolism, enhanced hippocampal cholinergic neurotransmission, improved cerebral perfusion and neuroprotection, reduced β-amyloid pathology, protected against oxidative damage, and improved cognition (learning and memory).[11-21]

With evidence of some effects of Souvenaid on memory in the early stages of AD,[22] a new study performed in patients with prodromal AD has been recently reported.[23] Previously, one report about the effects of Souvenaid in AD using meta-analysis did not show beneficial effects in terms of cognitive changes or functional ability.[24] However, this study performed the meta-analysis only using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[25] and the Alz-

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heimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale.[26] Although in a new randomized controlled trial (RCT) performed in prodromal AD, Souvenaid had no beneficial effect on the primary endpoint of the neuropsychological test battery (NTB)[27] over 2 years, secondary endpoints of disease progression measuring cognition, function, and hippocampal atrophy differed between groups.[23] With various outcome measurements including the NTB in a new RCT, the additional meta-analyses of outcome measures other than ADAS-Cog and ADCS-ADL could be possible.

We conducted this review and meta-analysis from all the RCTs on the effects of Souvenaid on cognition and functional abilities, with additional outcome measurements, with the hypothesis that Souvenaid may have beneficial effects in certain groups, especially with the suitable outcome measures, study duration, and disease states.

METHODS

Data sources, search strategy, and selection criteria

We searched Medline, Embase, Web of Science, CINAHL, and the Cochrane Library database in May 2020. Search terms used were: 'Alzheimer disease', 'Alzheimer dementia', 'mild cognitive impairment', 'cognitive dysfunction', 'Souvenaid', 'Fortasyn Connect', and derivatives of these (see online Supplementary Appendix 1 for further details on search strategy). We did not apply limits for the publication language, time, or status.

Two reviewers (YSS and BY) independently decided whether to include each study or not based on our predefined inclusion and exclusion criteria and assessed the reporting quality of the included studies by using the revised Cochrane risk of bias 2.0 tool,[28] which examines the following domains: bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcomes, bias in selection of the reported results, and overall risk of bias judgment. Any discrepancies were resolved by discussion between the reviewers.

Data extraction

The two reviewers independently performed data extraction using a predefined data extraction form. Any disagreements unresolved by discussion were resolved through review by a third author (DWY or SHN).

Only double-blind RCTs were included in this review and meta-analysis. The outcome measurements were cognition, clinical global change, functional ability and behavior, and adverse events. The duration of treatment was not restricted, but trials combined with other types of nutritional therapy or performed with patients who did not have AD were excluded.

After searching each database, we identified 86 citations, out of which full-text articles of eight studies were reviewed for eligibility (Figure 1). Four studies[29-32] were excluded because three used outcomes other than cognitive and functional abilities and one was an open-labeled extension study of a primary RCT already included in the review. Secondary analyses of primary studies included in the review can be easily excluded by screening titles and abstracts. Also, one RCT was excluded by screening its abstract, because the study participants were patients

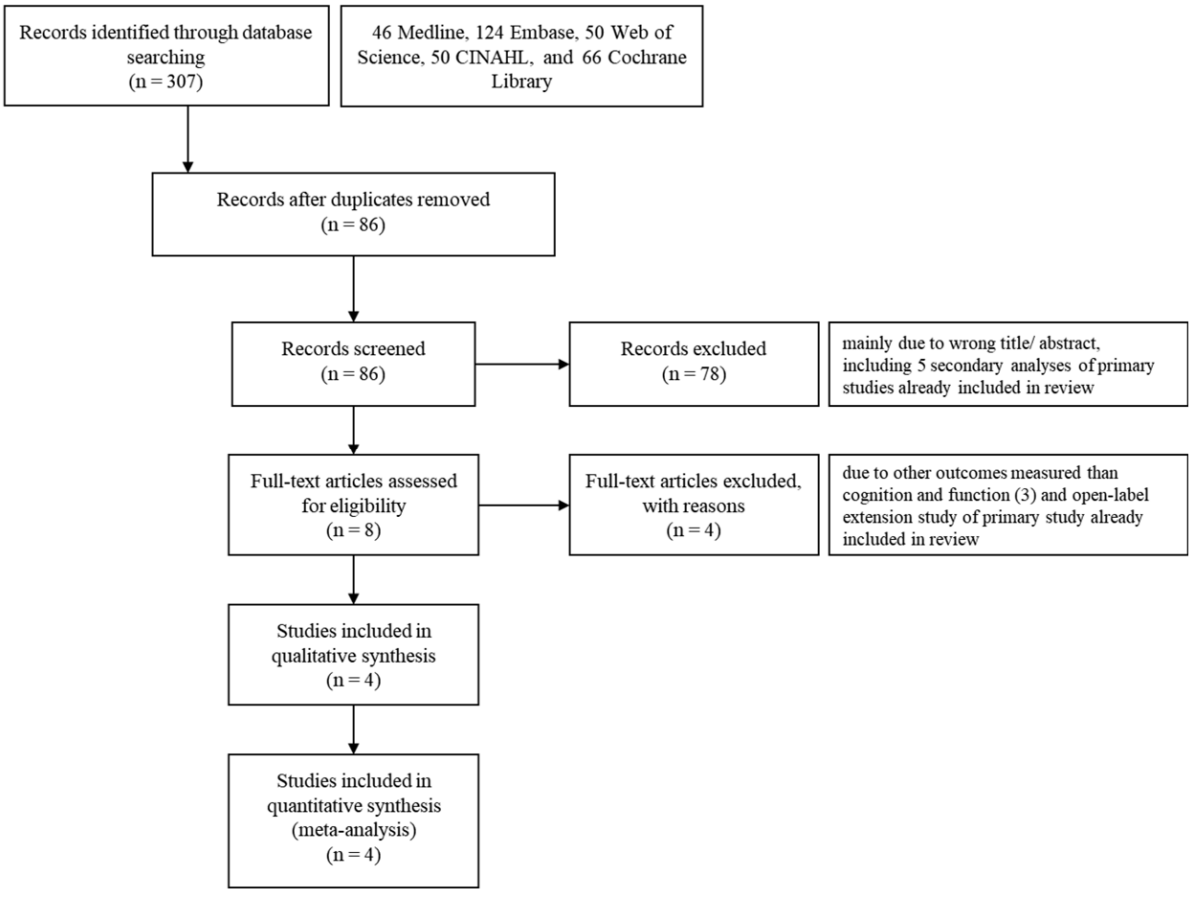

Figure 1. Flow chart for the inclusion of randomized controlled trials evaluating the effect of Souvenaid in Alzheimer's disease.

with frontotemporal dementia.[33] Thus, this review and meta-analysis included four RCTs[22,23,34,35] with a total of 1322 participants.

Assessment of methodology quality

Two reviewers independently assessed the methodologic qualities of each study using the risk of bias for an interrupted time series studies method suggested by the Cochrane Effective Practice and the Organisation of Care Group.[36] We assessed possible publication bias using the symmetry/asymmetry of funnel plots.

Statistical analysis

Review Manager 5.3 (Review Manager [RevMan; Computer program], Version 5.3, Copenhagen: The Nordic Cochrane Center, the Cochrane Collaboration, 2014) was used for the standard meta-analysis, using the random-effect model. Outcomes are only pooled if they are reported by more than two studies. Mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes and odds ratios (ORs) with 95% CIs for dichotomous outcomes were used to express the intervention effects. The heterogeneity of the outcomes across the studies was assessed using the Cochrane Q χ^2 statistic and I^2 statistic, the former with p values and the latter considered to indicate significant heterogeneity if greater than 50%. Funnel plots were used to evaluate publication bias.

RESULTS

Included studies

Figure 1 shows the flow chart for the inclusion of RCTs evaluating the effect of Souvenaid in AD. Table 1 presents study characteristics, patient populations, and results for Souvenaid. There were some variations in outcome measures, treatment duration, and disease stage included. For outcomes, cognitive function was measured with immediate (logical) and delayed verbal recalls of the Wechsler Memory Scale-revised (WMS-r) test,[37] ADAS-Cog, NTB, and a cognitive test battery.[38] Function and behavior were assessed using ADCS-ADL, quality of life,[39] a neuropsychological inventory (NPI),[40] and disability assessment in dementia.[41] The clinical global change was measured using the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus)[42] and the Clinical Dementia Rating scale-Sum of Boxes (CDR-SB).[43] The treatment duration in the RCTs was various, between 12 weeks (Souvenir I) and 24 months (LipiDiDiet). The LipiDiDiet was the study performed at the prodromal stage of AD, in contrast to the others, the Souvenir I and II in mild AD and the S-Connect study in mild to moderate AD. Contrary to the other three RCTs, the S-Connect study allowed participants to take cholinesterase inhibitors (ChEIs) and/or memantine as concomitant medications.

The overall quality of the four included RCTs was good (Figure 2). All of the studies properly reported on the randomization process, assignment to interventions, starting and adhering to interventions, the assessment of the outcome, and the reported outcome data. Two studies had some concerns of bias in the measurement of the outcome.[22,23] One had a baseline imbalance of MMSE score, which was adjusted for as a covariate in the analysis.[23] There was a low risk of bias due to deviations from intended interventions, bias due to missing outcome data, bias in the selection of the reported results, and overall bias.

Outcome measures: Cognition

Two studies (Souvenir I and S-Connect) reported cognitive function using the ADAS-Cog score, and the other two studies (Souvenir II and LipiDiDiet) used the Z-scores of the NTB. The meta-analysis of the ADAS-Cog score (Figure 3A) did not reveal a difference between groups (n=727, MD=0.08, 95% CI=−0.71-0.88, I^2=0%). The meta-analysis (Figure 3B) of the NTB Z-scores also showed no differences in total (n=446, MD=0.05, 95% CI=-0,02-0.12, I^2=27%), memory domain (n=480, MD=0.11, 95% CI=0.02-0.20, I^2=0%), or executive function domain (n=466, MD=-0.03, 95% CI=-0.17-0.12, I^2=74%).

However, some results were promising. The Souvenir I study reported a higher proportion of participants with improved WMS-r delayed verbal recall tests in the Souvenaid group compared with the placebo group (40% vs. 24%, p=0.02). Moreover, in a subgroup of very mild AD with mini-mental state examination (MMSE)[44] scores of 24-26, improvements in the WMS-r delayed (p=0.011) and immediate (p=0.033) verbal recalls were reported in the Souvenaid group.[22] In the Souvenir II study, the NTB memory domain Z-score was increased in the Souvenaid group (p=0.023).[35] Although the LipiDiDiet reported no difference in the primary outcome of the NTB memory domain z-score between the Souvenaid and the placebo groups (0.20±0.40 vs 0.11±0.46, p=0.09), there was an increase in the NTB total composite z-score in the Souvenaid group compared with the placebo group (0.120±0.278 vs 0.035±0.286, p=0.035).[23] The predefined subgroup (MMSE score ≥26) in the LipiDiDiet trial showed differences in favor of the Souvenaid group in the NTB composite and memory domain scores, as well as in CDR-SB. However, the S-Connect study did not show any differences in the cognitive measures.[34]

Outcome measures: Global clinical function, functional ability, and behavior

The S-Connect and LipiDiDiet studies assessed CDR-SB scores as outcome measures for global clinical function. The meta-analysis (Figure 4) showed no difference in CDR-SB scores between the Souvenaid and placebo groups (n=739, MD=-0.21, 95% CI=−0.47-0.06, I^2=82%). However, in the LipiDiDiet study, taking Souvenaid had beneficial effects on the CDR-SB. In the Souvenir I study, after 12 weeks, the percentage of responders as measured using three criteria, ADAS-Cog ≥4 points decline, ADCS-ADL score ≥4 points increase, and CIBIC-plus "improvement", was greater in the Souvenaid group (18.2% vs 7.2%; p=0.031).

The Souvenir I and S-Connect studies measured functional ability using ADCS-ADL scores. The meta-analysis for the ADCS-ADL score (Figure 5) showed no difference in the Souvenaid group compared with the placebo group (n=739, MD=0.36, 95% CI=−0.54-1.25, I^2=0%). Because of discrepancies in the measurements of functional ability and behavior across the trials, the meta-

Table 1. Characteristics of included randomized controlled trials evaluating the effectiveness of Souvenaid in Alzheimer's disease

Study	Methods 1) Study design 2) Duration	Patients 1) Diagnosis 2) Inclusion criteria 3) No. of Patients 4) Age (mean±SD)	Intervention (Placebo)	Outcomes
Scheltens P et al., 2010[22] Souvenir I in The Netherlands (11), Germany (11), Belgium (5), United Kingdom (1), and United States (1)	1) DB-RCT 2) 12 weeks	1) drug-naive, mild AD, NINCDS-ADRDA 2) age ≥50 years, MMSE 20-26 3) 225 (212 efficacy data) 4) 73.3±7.8 (control) vs 74.1±7.2 (active)	125ml Souvenaid once-daily (Isocaloric milk drink)	· Primary outcomes: change from baseline on the delayed verbal recall test of the WMS-r; and the 13-item modified ADAS-Cog · Secondary Outcomes: 24-week change from baseline on modified ADAS-cog and WMS-r delayed verbal recall task, and change at 12 and 24 weeks on MMSE and WMS-r immediate verbal memory task; CIBIC-plus; 12-item NPI; ADCS-ADL; QoL-AD; plasma homocystein and vitamins C and E, and erythrocyte membrane fatty acid profile
Shah RC et al., 2013[34] S-Connect in the United States (48)	1) DB-RCT 2) 24 weeks	1) mild-to-moderate AD taking dementia medications, NINCDS-ADRDA 2) age ≥50 years, MMSE 14-24 3) 527 4) 76.7±8.2	125ml Souvenaid once-daily (Isocaloric milk drink)	· Primary outcome: the 11-item ADAS-cog · Secondary outcomes: cognitive test battery, the 23-item ADCS-ADL, CDR-SB
Scheltens P et al., 2014[35] Souvenir II in The Netherlands (9), Germany (5), Belgium (4), Spain (3), Italy (3), and France (3)	1) DB-RCT 2) 24 weeks	1) drug-naïve, mild AD, NINCDS-ADRDA 2) age ≥50 years, MMSE ≥20 3) 259 4) 73.2±8.4 (control) vs 74.4±6.9 (active)	125ml Souvenaid once-daily (Isocaloric milk drink)	· Primary outcome: the NTB memory function domain score (z-score) · Secondary outcomes: the executive function domain score based on the NTB (z-score), total NTB composite score, individual item scores from the NTB, DAD, nutritional blood parameters, and EEG
Soininen H et al., 2017[23] LipiDiDiet in 11 sites in Finland, Germany, the Netherlands, and Sweden	1) DB-RCT 2) 24 months	1) prodromal AD, IWG-1 2) age 55-85 years, MMSE ≥24, (≥20 if education level ≤6 years) 3) 311 4) 70.7±6.2 (control) vs. 71.3±7.0 (active)	125ml Souvenaid once-daily (Isocaloric milk drink)	· Primary outcome: change in the NTB composite score · Secondary outcomes: the NTB memory and executive function domain, the NTB total, CDR-SB, brain volumes based on MRI, progression to dementia, serum concentrations of HDL and LDL cholesterols, plasma fatty acids, and DHA in CSF

Table 1. Characteristics of included randomized controlled trials evaluating the effectiveness of Souvenaid in Alzheimer's disease (cont.)

Study	Results
Scheltens P et al., 2010[22]	· Improvement in WMS-r delayed verbal recall in the active group (p=0.021). · Unchanged other outcome scores. · At 12 weeks, 40% of patients in the active group showed an improvement in WMS-r delayed recall compared with 24% in the control group; and the percentage of patients defined as responders was greater in the active group (18.2% vs 7.2%; p=0.031). · In the prespecified subgroup analysis of patients with very mild AD (MMSE 24-26; n=120), the active group showed an improvement in WMS-r delayed verbal recall compared with controls (p=0.011).
Shah RC et al., 2013[34]	· No differences between study groups over 24 weeks.
Scheltens P et al., 2014[35]	· Differences of the NTB memory domain z-score between groups (p=0.023). · Trend for an effect on the NTB total composite score (p=0.053). · No effect on the NTB executive function domain and DAD.
Soininen H et al., 2017[23]	· No differences between groups for the primary endpoint. · For CDR-SB, less worsening in the active group (p=0.005). Les reduction in hippocampal volume (p=0.005) and less increase in ventricular volume (p=0.046). · Predefined subgroup analysis (MMSE ≥26), significant differences between groups for CDR-SB and hippocampal volume in the mITT population, and for the NTB primary endpoint and the NTB memory domain in the per-protocol population.

SD: standard deviation; DB-RCT: double blind: randomized controlled trial; AD: Alzheimer's disease; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; MMSE: Mini-mental state examination; WMS-r: delayed verbal recall test of the Wechsler Memory Scale–revised; ADAS-Cog: Alzheimer's Disease Assessment Scale–cognitive subscale; CIBIC-plus: Clinician Interview Based Impression of Change plus Caregiver Input; NPI: Neuropsychiatric Inventory; ADCS-ADL: Alzheimer's disease Co-operative Study–Activities of Daily Living; QOL: Quality of life; CDR-SB: Clinical Dementia Rating scale—Sum of Boxes; NTB: neuropsychological test battery; DAD: disability assessment for dementia scale; EEG: electroencephalography; IWG: international working group; MRI: magnetic resonance imaging; HDL: high-density lipoprotein; LDL: low-density lipoprotein; DHA: Docosahexaenoic acid; CSF: Cerebrospinal fluid; mITT: modified intention to treat.

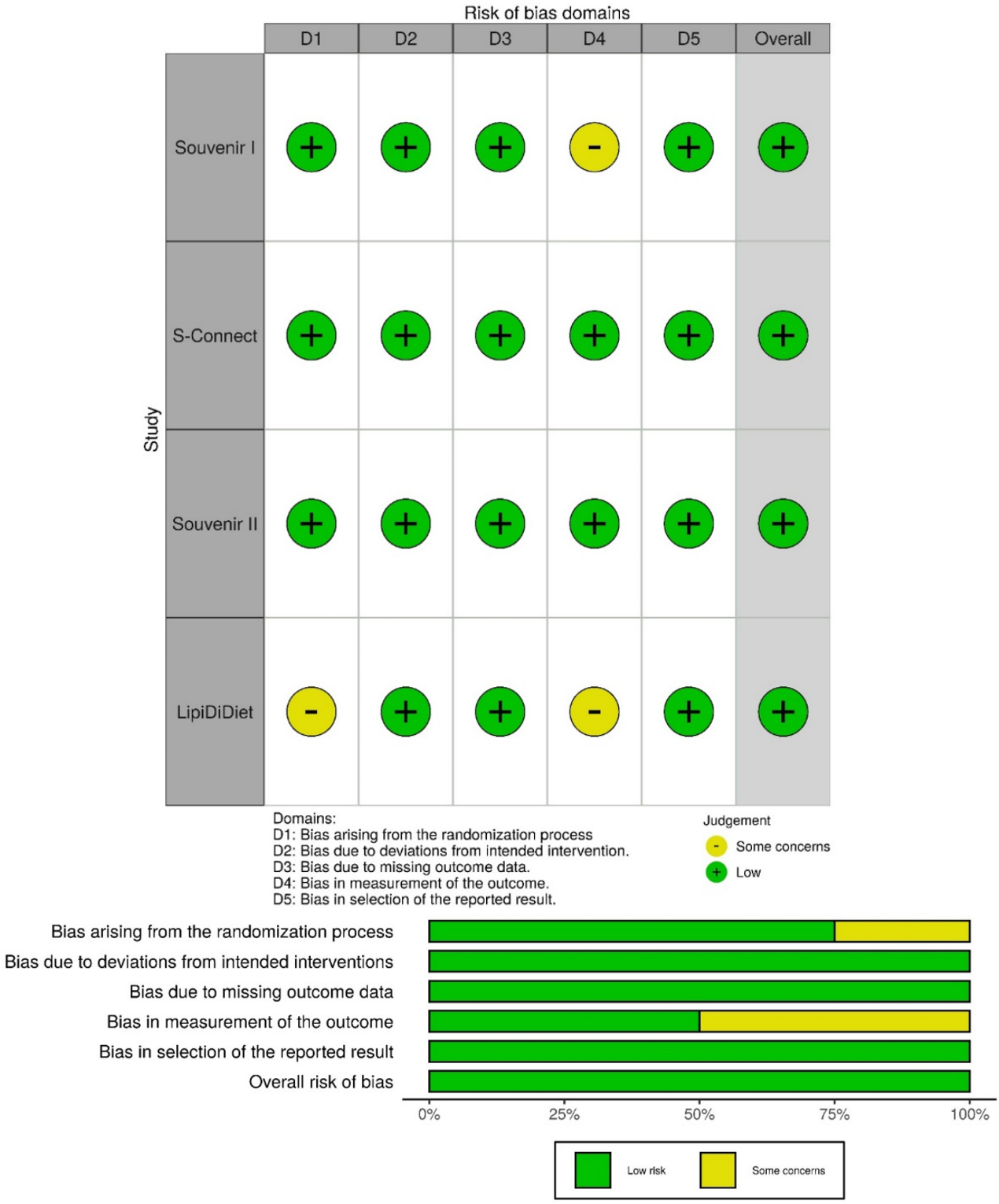

Figure 2. (A) Risk of bias summary of randomized controlled trials (RCTs) examining the effect of Souvenaid in Alzheimer's disease (AD). (B) Risk of bias graph of RCTs examining the effect of Souvenaid in AD.

analysis of results using these different outcome measures was considered inappropriate. In the Souvenir I study, there was no difference in the changes in NPI scores between groups.

Outcome measures: Adverse events, adherence, and compliance

Meta-analyses (n=1321, Figure 6) did not show differences in any adverse events (OR=0.84, 95% CI=0.63-1.12, I^2=28%) or in serious adverse events (OR=0.95, 95% CI=0.66-1.36, I^2=9%). Souvenaid was well tolerated over all the RCTs. There were no differences in drop-out rates between groups. Compliances were high across all the RCTs. Also, in a 24-month long-term trial (LipiDiDiet), none of the serious adverse events were regarded as related to Souvenaid and the dropout rate due to adverse events did not differ between groups.

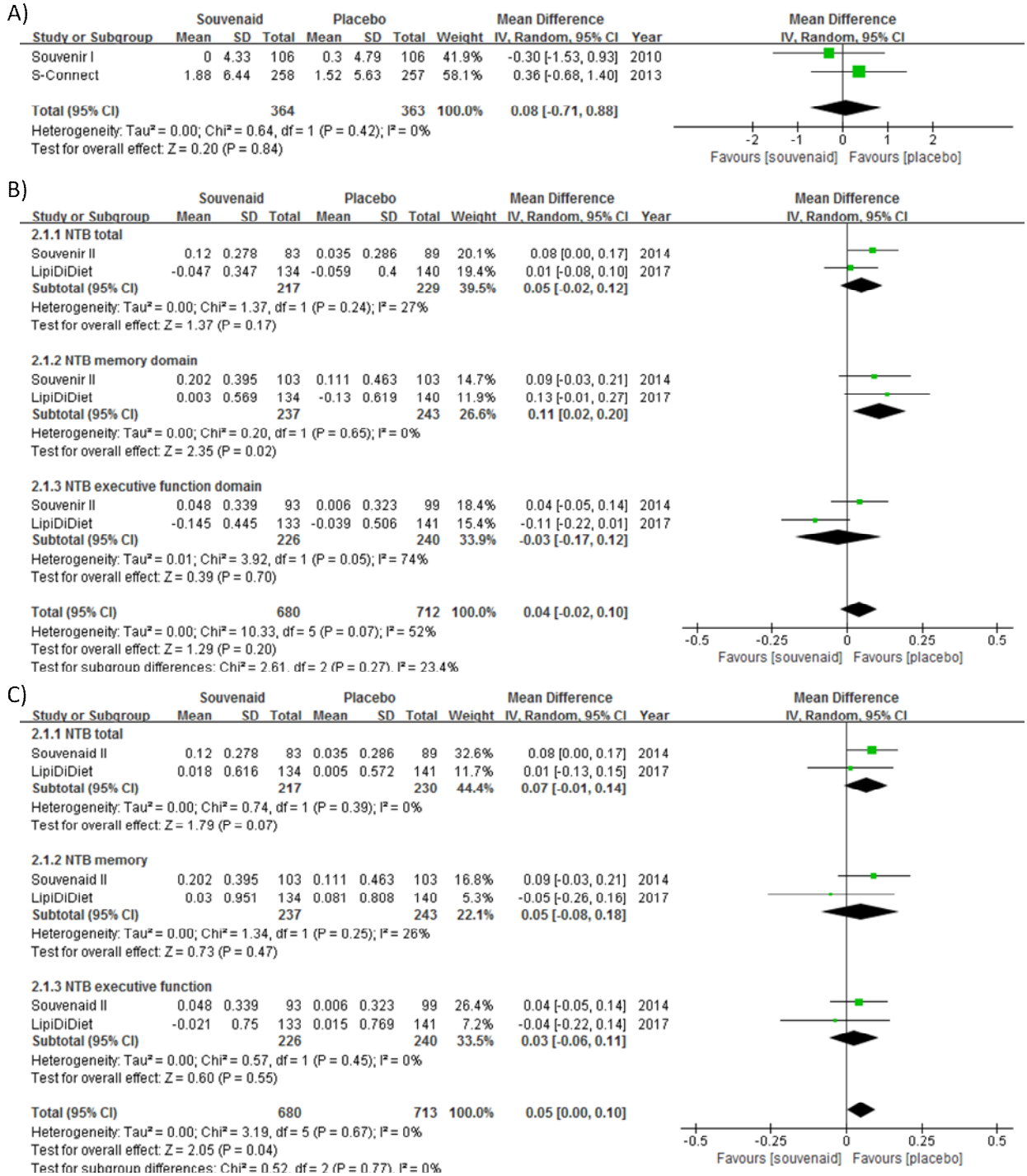

Figure 3. Effect of Souvenaid supplementation of cognition measured by (A) ADAS-Cog and (B) NTB scores, and (C) NTB scores at 6-month follow-up. ADAS-Cog, Alzheimer's Disease Assessment Scale–cognitive subscale; NTB, neuropsychological test battery.

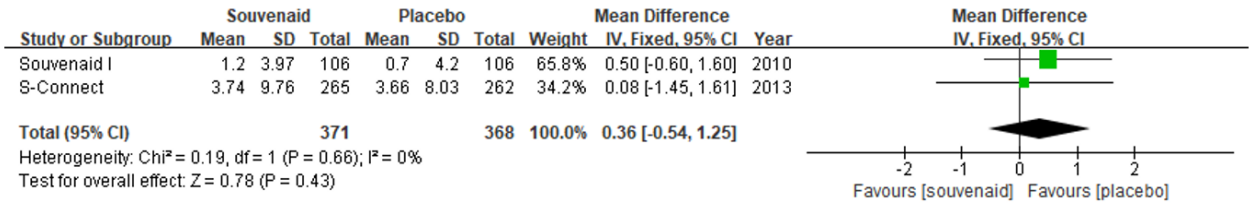

Figure 4. Effect of Souvenaid supplementation on functional ability measured by ADCS-ADL. ADCS-ADL, Alzheimer's disease Co-operative Study–Activities of Daily Living.

DISCUSSION

This review shows that Souvenaid had no significant effects on cognition measured by the ADAS-Cog and the NTB scores, global clinical function measured by CDR-SB, or functional ability measured by the ADCS-ADL scores, based on our meta-analyses.

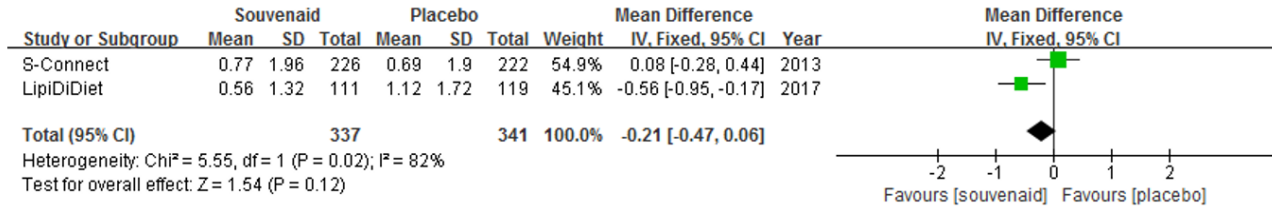

Figure 5. Effect of Souvenaid supplementation on global clinical function measured by CDR-SB. CDR-SB, Clinical Dementia Rating scale—Sum of Boxes

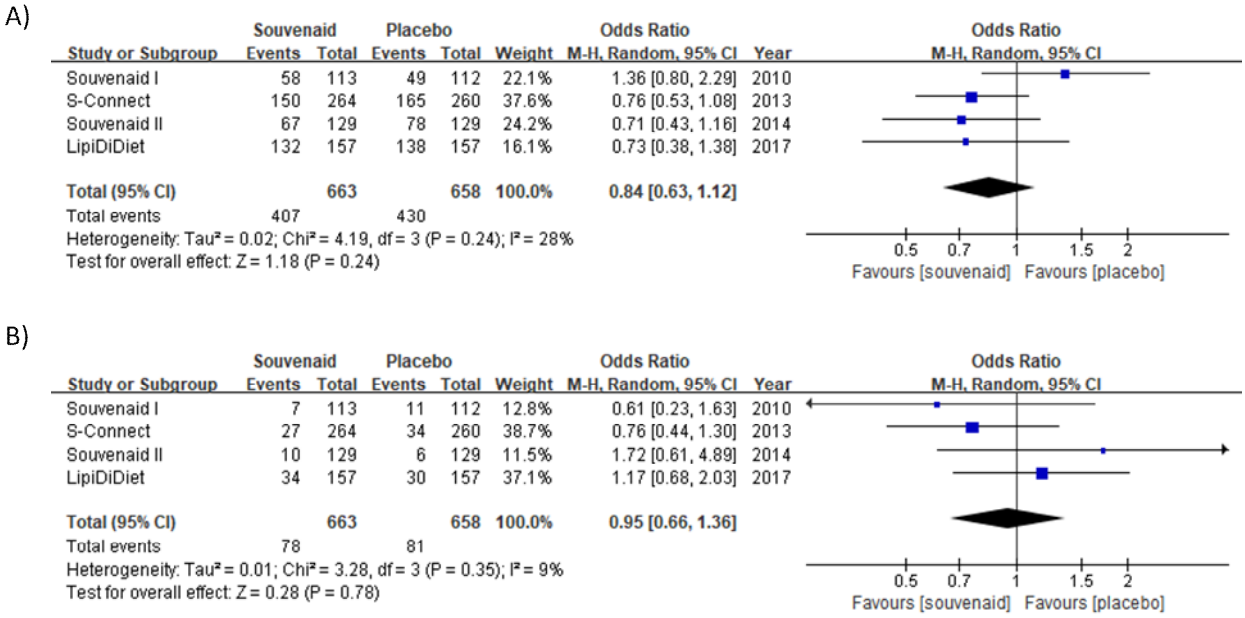

Figure 6. (A) Any and (B) serious adverse events after Souvenaid supplementation

The Souvenaid RCTs showed inconsistent results. The Souvenir I study, performed at the mild stage of AD, showed beneficial effects on memory function represented by the delayed verbal recall subscale of the WMS-r and the ADAS-Cog score, but the ADAS-Cog score did not differ in the S-Connect study performed at the mild to moderate stage of AD. In the Souvenir II study, which was also performed at the mild stage of AD, there were improvements on the NTB memory domain Z-score, but the S-Connect study, which was performed at the mild to moderate stages of AD, did not show any difference. Unfortunately, the LipiDiDiet study did not show beneficial effects on the NTB composite score in the primary outcome. However, in the LipiDiDiet study, a predefined subgroup (MMSE ≥26) showed favorable outcomes in the NTB memory domain score, in addition to the CDR-SB and MRI hippocampal volume, which already exhibited beneficial effects in the original analysis. Although participants taking Souvenaid showed beneficial effects on CDR-SB in the LipiDiDiet study, Souvenaid had no other beneficial effects on function, behavior, or clinical global change across all the other RCTs.

Similar to the above results of the RCTs, reviews about vitamin B and omega-3 fatty acids, which are contents of Souvenaid, also suggest that this nutritional support may have some beneficial effects on cognition, especially the memory domain, in patients with mild AD.[45,46] In contrast to the Souvenir I and II studies, the S-Connect study included patients with mild-to-moderate AD (MMSE 14–24) taking ChEIs and/or memantine. Souvenaid did not result in additional benefits on cognitive, functional, or global outcomes. The previous review showed that diets supplemented with ChEIs had no additional beneficial effects on cognitive function in AD.[47]

With the hope that Souvenaid may have some benefits for cognition, especially in patients at the early stages of AD, a new RCT was performed in patients with prodromal AD. However, Souvenaid did not show beneficial effects in preventing progression in patients with prodromal AD. However, in the LipiDiDiet trial, the Souvenaid group showed less reduction in hippocampal volume (26% less reduction) and less increase in ventricular volume (16% less increase). Moreover, in a secondary analysis of the Souvenir II study using electroencephalography data for the construction of brain networks, the Souvenaid group showed greater preservation of the networks, indicating a potential benefit on synaptic integrity and function.[29] Souvenaid in mild AD has been shown to improve local and global brain network connectivity,[29] which are thought to correlate with memory function.

There are some limitations in the study. Because of the variations in the outcome measurements used in the trials, we could only conduct the meta-analyses using the outcome measures included in just 2-3 studies. We could not find unified outcome measures across all of the RCTs. For example, CDR-SB was used in the S-Connect and

LipiDiDiet studies, and ADCS-ADL and ADAS-Cog were used only in the Souvenir I and the S-Connect trials. A unified assessment would be helpful for a more reliable analysis. The ADAS-Cog has been used commonly as the standard measure of cognition in AD clinical trials. However, recent trials performed in early stages of the disease have shown some limitations of ADAS-Cog, which could not be useful in early stages of AD, including MCI, because it did not include assessment of the cognitive domains such as attention and executive function, which were most affected in the early stages of AD.[48] In addition, it will be better to evaluate respectively the individual domains most likely to be affected, such as memory and executive function, rather than the NTB composite score assessing all domains together.

Furthermore, it will be considered similarly for functional outcomes in patients with early stages of AD. Currently, CDR-SB is widely used in clinical trials for patients with prodromal AD, as it has small floor and ceiling effects and reflects real-life activities well.[48] Next, we could not perform sensitivity or subgroup analyses, due to the small number of studies and participants. Studies with larger sample sizes would be helpful. Various factors such as the duration of treatment, disease stage, and so on should be considered for further studies. Confirmation of biomarkers such as amyloid PET could strengthen the study results.

Although the meta-analysis of the four clinical trials of Souvenaid did not show any clinical benefits in AD, the overall positive impression is that Souvenaid may have benefits on domains of cognition that are affected by AD (attention, memory, and executive function), and that it may have greater potential for benefit earlier rather than later in the disease. Further studies with outcome measures suitable in patients with early stages of AD will be needed.

Conclusions

The results of current clinical trials do not suggest that Souvenaid has any beneficial effects on functional ability, behavior, or global clinical change. However, Souvenaid may have benefits on cognition, especially attention, memory, and executive function, which are impaired early in AD. This suggests that Souvenaid may have greater potential for benefits earlier rather than later in the disease. Further studies with outcome measures suitable for evaluating patients with early stages of AD are needed.

AUTHOR DISCLOSURES

The authors have no conflicts of interest to declare.

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Database	No.	Search query	Search Results (2020.05.26)	Note
PubMed	#1	"Alzheimer disease"[Mesh]	92,702	
	#2	"Alzheimer dementia"[TIAB] OR "Alzheimer's disease"[TIAB]	118,422	
	#3	"Cognitive dysfunction"[Mesh]	16,633	
	#4	"mild cognitive impairment"[TIAB] OR "mild neurocognitive disorder"[TIAB]	16,819	
	#5	**#1 OR #2 OR #3 OR #4**	**159,564**	**P - MCI, Alzheimer's disease**
	#6	"Fortasyn Connect"[TIAB] OR "Fortasyn Connect"	25	
	#7	"Souvenaid"[TIAB] OR "Souvenaid"	37	
	#8	"Souvenir"[TIAB] OR "Souvenir"	199	
	#8	**#6 OR #7 OR #8**	**243**	**I - Souvenaid**
	#9	**#5 AND #8**	**46**	**P AND I**

Database	No.	Search query	Search Results (2020.05.26)	Note
EMBASE (Elsevier)	#1	'alzheimer disease'/exp	198,161	
	#2	'alzheimer dementia':ti,ab OR 'alzheimer disease':ti,ab	22,455	
	#3	'mild cognitive impairment'/exp	26,535	
	#4	'cognitive dysfunction':ti,ab OR 'cognitive dysfunctions':ti,ab OR 'cognitive defect':ti,ab	22,272	
	#5	**#1 OR #2 OR #3 OR #4**	**231,705**	**P - MCI, AD**
	#6	'souvenaid'/exp	720	
	#7	'fortasyn AND connect':ti,ab	-	
	#8	'souvenaid':ti,ab	110	
	#8	**#6 OR #7 OR #8**	**805**	**I - Souvenaid**
	#10	**#5 AND #8**	**124**	**P AND I**

Database	No.	Search query	Search Results (2020.05.26)	Note
CochraneLibrary (Wiley)	#1	[mh "alzheimer disease"]	3,307	
	#2	"alzheimer dementia":ti,ab,kw OR "alzheimer disease":ti,ab,kw	9,779	
	#3	[mh ^"Cognitive Dysfunction"]	1,305	
	#4	"Cognitive Dysfunction":ti,ab,kw OR "Cognitive Dysfunctions":ti,ab,kw	3,010	
	#5	**#1 OR #2 OR #3 OR #4**	**12,428**	**P - MCI, AD**
	#6	"fortasyn connect":ti,ab,kw	37	
	#7	"souvenaid":ti,ab,kw OR "souvenir":ti,ab,kw	86	
	#8	**#6 OR #7**	**90**	**I - Souvenaid**
	#9	**#5 AND #8**	**66**	**P AND I**

Database	No.	Search query	Search Results (2020.05.26)	Note
CINAHL	#1	Alzheimer dementia	25,217	
	#2	Alzheimer's disease or Alzheimer disease	42,299	
	#3	mild cognitive impairment	7,314	
	#4	#1 OR #2 OR #3	46,085	P - MCI, Alzheimer's disease
	#5	souvenaid	18	
	#6	fortasyn connect	8	
	#7	**#5 OR #6**	**21**	**I - Souvenaid**
	#8	**#4 AND #7**	**21**	**P AND I**

Database	No.	Search query	Search Results (2020.05.26)	Note
Web of Science	#1	TS=Alzheimer's disease	118,272	
	#2	TS=Alzheimer dementia	48,548	
	#3	TS=mild cognitive impairment	33,774	
	#4	**#1 OR #2 OR #3**	**143,282**	**P - MCI, AD**
	#5	TS=souvenaid	44	
	#6	TS=fortasyn connect	25	
	#7	**#5 OR #6**	**55**	**I - Souvenaid**
	#8	**#4 AND #7**	**50**	**P AND I**

Supplementary figure 1. Search strategies of each database.

Domain	Assessment tool	Characteristics
Cognition	WMS-r test	provide an estimation of overall memory function
	ADAS-Cog	be used to assess the severity of cognitive symptoms of dementia, and one of the most widely used cognitive scales in clinical trials
Function and behavior	ADCS-ADL	assess the competence of patients with AD in basic and instrumental activities of daily living
	QOL-AD	provide both a patient and a caregiver report of the quality of life for patients who have been diagnosed with AD
	NPI	assess dementia-related 12 behavioral and psychological symptoms
	DAD	be developed for a disability measure designed specifically for community-dwelling individuals with dementia of the Alzheimer type
Clinical global change	CIBIC-plus	include data on the patients' history, general appearance, mental cognitive stage, behavior, functional ability, and 7-point scales recording disease severity and changes during and/or at the end of treatment
	CDR	be used in clinical and research settings to stage dementia severity, and rated in 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care

Supplementary figure 2. Characteristics and functions of the assessment tools.