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Multi-domain interventions for the prevention of dementia and cognitive decline (Review)

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[Intervention Review]

Multi-domain interventions for the prevention of dementia and cognitive decline

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ABSTRACT

Background

Dementia is a worldwide concern. Its global prevalence is increasing. Currently, no effective medical treatment exists to cure or to delay the onset of cognitive decline or dementia. Up to 40% of dementia is attributable to potentially modifiable risk factors, which has led to the notion that targeting these risk factors might reduce the incidence of cognitive decline and dementia. Since sporadic dementia is a multifactorial condition, thought to derive from multiple causes and risk factors, multi-domain interventions may be more effective for the prevention of dementia than those targeting single risk factors.

Objectives

To assess the effects of multi-domain interventions for the prevention of cognitive decline and dementia in older adults, including both unselected populations and populations at increased risk of cognitive decline and dementia.

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's register, MEDLINE (Ovid SP), Embase (Ovid SP), PsycINFO (Ovid SP), CINAHL (EBSCOhost), Web of Science Core Collection (ISI Web of Science), LILACS (BIREME), and ClinicalTrials.gov on 28 April 2021. We also reviewed citations of reference lists of included studies, landmark papers, and review papers to identify additional studies and assessed their suitability for inclusion in the review.

Selection criteria

We defined a multi-domain intervention as an intervention with more than one component, pharmacological or non-pharmacological, but not consisting only of two or more drugs with the same therapeutic target. We included randomised controlled trials (RCTs) evaluating the effect of such an intervention on cognitive functioning and/or incident dementia. We accepted as control conditions any sham intervention or usual care, but not single-domain interventions intended to reduce dementia risk. We required studies to have a minimum of 400 participants and an intervention and follow-up duration of at least 12 months.

Data collection and analysis

We initially screened search results using a 'crowdsourcing' method in which members of Cochrane's citizen science platform identify RCTs. We screened the identified citations against inclusion criteria by two review authors working independently. At least two review authors also independently extracted data, assessed the risk of bias and applied the GRADE approach to assess the certainty of evidence. We defined high-certainty reviews as trials with a low risk of bias across all domains other than blinding of participants and personnel involved in administering the intervention (because lifestyle interventions are difficult to blind). Critical outcomes were incident dementia,

incident mild cognitive impairment (MCI), cognitive decline measured with any validated measure, and mortality. Important outcomes included adverse events (e.g. cardiovascular events), quality of life, and activities of daily living (ADL). Where appropriate, we synthesised data in random-effects meta-analyses. We expressed treatment effects as risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs).

Main results

We included nine RCTs (18.452 participants) in this review. Two studies reported incident dementia as an outcome; all nine studies reported a measure for cognitive functioning. Assessment of cognitive functioning was very heterogeneous across studies, ranging from complete neuropsychological assessments to short screening tests such as the mini-mental state examination (MMSE). The duration of the interventions varied from 12 months to 10 years.

We compared multi-domain interventions against usual care or a sham intervention. Positive MDs and RRs <1 favour multi-domain interventions over control interventions. For incident dementia, there was no evidence of a difference between the multi-domain intervention group and the control group (RR 0.94, 95% CI 0.76 to 1.18; 2 studies; 7256 participants; high-certainty evidence). There was a small difference in composite Z-score for cognitive function measured with a neuropsychological test battery (NTB) (MD 0.03, 95% CI 0.01 to 0.06; 3 studies; 4617 participants; high-certainty evidence) and with the Montreal Cognitive Assessment (MoCA) scale (MD 0.76 point, 95% CI 0.05 to 1.46; 2 studies; 1554 participants), but the certainty of evidence for the MoCA was very low (due to serious risk of bias, inconsistency and indirectness) and there was no evidence of an effect on the MMSE (MD 0.02 point, 95% CI -0.06 to 0.09; 6 studies; 8697participants; moderate-certainty evidence). There was no evidence of an effect on mortality (RR 0.93, 95% CI 0.84 to 1.04; 4 studies; 11,487 participants; high-certainty evidence).

There was high-certainty evidence for an interaction of the multi-domain intervention with ApoE4 status on the outcome of cognitive function measured with an NTB (carriers MD 0.14, 95% CI 0.04 to 0.25, noncarriers MD 0.04, 95% CI -0.02 to 0.10, P for interaction 0.09). There was no clear evidence for an interaction with baseline cognitive status (defined by MMSE-score) on cognitive function measured with an NTB (low baseline MMSE group MD 0.06, 95% CI 0.01 to 0.11, high baseline MMSE group MD 0.01, 95% CI -0.01 to 0.04, P for interaction 0.12), nor was there clear evidence for an effect in participants with a Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score > 6 points (MD 0.07, 95%CI -0.00 to 0.15).

Authors' conclusions

We found no evidence that multi-domain interventions can prevent incident dementia based on two trials. There was a small improvement in cognitive function assessed by a NTB in the group of participants receiving a multi-domain intervention, although this effect was strongest in trials offering cognitive training within the multi-domain intervention, making it difficult to rule out a potential learning effect. Interventions were diverse in terms of their components and intensity.

PLAIN LANGUAGE SUMMARY

Prevention of dementia and decline in cognition by using multi-domain interventions

Review question

Can cognitive decline and dementia be prevented by interventions which target two or more risk factors for dementia?

Background

Dementia is a condition in which memory and other thinking skills (known as cognition, or cognitive functioning) decline to the point that they affect a person's ability to be fully independent in their daily activities. It can be caused be a variety of different brain problems, most of which become increasingly common with age. Although the risk of dementia increases for everyone as they get older, not everyone is at equal risk. A number of risk factors have been identified that make dementia more likely. These include high blood pressure in middle age, diabetes, smoking, drinking a lot of alcohol and lack of exercise. If these risk factors are addressed, then it might be possible to prevent some cognitive decline and dementia, or at least to delay its onset. Because dementia is a complex condition and there are many different risk factors, it may not be very effective to target only one risk factor. In this review, we are interested in interventions which aim to modify at least two risk factors; these are known as multi-domain interventions.

Study characteristics

We searched up to 28 April 2021 for studies in which people without dementia were randomly assigned to a multi-domain intervention or to usual health care (for example general health advice) and the groups were later compared by counting the number of people who had developed dementia or by measuring cognitive functioning. We found nine studies with a total of 18,452 participants. The average age of the participants was 68 years. The studies differed in several important ways, including in the risk factors they tried to modify, in how long the interventions lasted (from 1 year up to 10 years), and in the tests used to measure cognitive functioning. All of the studies took place in high- or middle-income countries in which usual health care was probably of a good standard.

Key results

Only two studies counted the number of people who developed dementia. Older adults receiving a multi-domain intervention were no more or less likely to develop dementia than those receiving usual care. Multi-domain interventions probably slightly improved cognitive functioning when this was measured with a long, detailed test, although we did not find any effect in studies that measured cognitive functioning with a short, screening test (the Mini-Mental State Examination, MMSE). The studies that found a benefit mostly offered cognitive training within the multi-domain intervention, making it possible that some of the effect could have been due to people getting better at performing cognitive tests, instead of being due to a real improvement in cognitive functioning that would be apparent in daily life. The effect was also stronger among participants who had an increased genetic risk for dementia (people carrying the ApoE4 gene). None of the studies reported harmful effects of the interventions.

We found that most studies were well-conducted. Overall, the certainty of the evidence was moderate to high, which means we are moderately to very confident in our results.

Our conclusions

We did not find evidence that multi-domain interventions can prevent dementia, but they may have a small beneficial effect on cognitive functioning in older people. There were a lot of differences between the interventions and we cannot say anything about whether targeting particular risk factors or combinations of risk factors might have a bigger effect, or about how long interventions might need to last. There is a still a lot than can be learned from further research in this area.

Summary of findings 1. Multi-domain interventions compared to usual care/placebo for the prevention of dementia and cognitive decline

Multi-domain interventions compared to usual care/placebo for the prevention of dementia and cognitive decline

Patient or population: community-dwelling older adults
Setting: community
Intervention: multi-domain interventions
Comparison: usual care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care/placebo	Risk with Multi-domain interventions				
Incidence of dementia	Study population		RR 0.94 (0.76 to 1.18)	7256 (2 RCTs)	⊕⊕⊕⊕ HIGH	Little or no effect of multi-domain interventions on incident dementia
	42 per 1.000	39 per 1.000 (32 to 49)				
Incidence of MCI	Study population		RR 0.97 (0.76 to 1.23)	3802 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	Probably no effect of multi-domain interventions on incident MCI
	66 per 1.000	64 per 1.000 (50 to 81)				
Cognitive decline measured with a NTB composite score (Z-score)		MD 0.03 SD higher (0.01 higher to 0.06 higher)	-	4617 (3 RCTs)	⊕⊕⊕⊕ HIGH	Small benefit of multi-domain interventions on cognitive decline measured with a NTB.
Cognitive decline measured with MMSE (range 0 to 30 points)		MD 0.02 point higher (0.06 lower to 0.09 higher)	-	8697 (6 RCTs)	⊕⊕⊕⊖ MODERATE [2]	Probably no effect of multi-domain interventions on cognitive decline measured with MMSE
Cognitive decline measured with MoCA (range 0 to 30 points)		MD 0.76 point higher (0.05 higher to 1.46 higher)	-	1554 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [2 3 4]	Very uncertain evidence whether multi-domain interventions improve cognitive decline measured with MoCA
Mortality	Study population		RR 0.93 (0.84 to 1.04)	11487 (4 RCTs)	⊕⊕⊕⊕ HIGH	Little or no effect of multi-domain interventions on mortality
	102 per 1.000	95 per 1.000				

		(86 to 107)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **MCI:** Mild cognitive impairment; **MD:** mean difference; **MMSE:** Mini-mental state examination; **MoCA:** Montreal cognitive assessment tool; **NTB:** neuropsychological test battery; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Only one study included in analysis; only studied in participants with history of diabetes (uncertain external validity)
[2] Used effect measure is validated as a screening tool and has not formally been developed to quantify cognitive decline over time
[3] Findings at serious risk of bias; no allocation concealment, no individual randomisation, no clear description of source population, unclear statistics used in included studies
[4] Serious heterogeneity detected

BACKGROUND

Description of the condition

Dementia is a clinical syndrome, usually chronic or progressive, and mainly affecting older adults. It is characterised by a decline in cognitive and functional ability, beyond what might be expected from normal ageing. Cognitive impairment occurs in the early stages of dementia, often accompanied by changes in behaviour. In the more advanced stages of dementia, most functional abilities become profoundly impaired, causing serious regression and ultimately complete dependency. Currently, there is no treatment available to slow down or cure dementia. Current estimates suggest that there are roughly 50 million people living with dementia worldwide, a number forecast to reach 75 million by 2030 and 131 million by 2050 (Prince 2015).

The most common form of dementia is Alzheimer's disease, accounting for up to 70% of dementia cases, followed by vascular dementia (WHO 2019). Other dementias include dementia with Lewy bodies, frontotemporal dementia, and dementia in Parkinson's disease; subtypes are often hard to distinguish, however, and mixed forms regularly co-exist.

Although age is the strongest risk factor, dementia is not an inevitable consequence of ageing. Dementia may be the end result of a variety of diseases and injuries that primarily or secondarily affect the brain. The pathophysiological chain of events leading to dementia often starts off years before the clinical onset of dementia becomes clear. Observational data have shown that up to 40% of all dementia is attributable to potentially modifiable risk factors, such as hypertension, high cholesterol, diabetes mellitus, unhealthy diet, and smoking (Barnes 2011; Norton 2014; Livingston 2017; Livingston 2020). Identification of these potentially modifiable risk factors has led to the notion that it may be possible to prevent or postpone the onset of dementia.

Description of the intervention

Although no disease-modifying treatment is currently available for established dementia, a delay in the onset of dementia would be beneficial for even the oldest adults (Tom 2015). In several single-domain intervention studies, especially testing the effectiveness of lifestyle interventions, a protective effect of dementia risk factor modification has been suggested (Andrieu 2015). The World Health Organisation (WHO) has identified several potentially modifiable domains that may hold potential for dementia risk reduction interventions, which we will briefly describe below (WHO 2019).

A number of studies have examined pharmacological interventions for dementia prevention. Several longitudinal studies, following participants for decades, have shown that many individuals developing dementia in late life had a history of high blood pressure in earlier life (Skoog 1996; Tzourio 2014). There is, however, a lack of convincing evidence that antihypertensive drugs have a favourable effect on dementia incidence and cognitive decline. Several meta-analyses have shown conflicting results of the effect of blood-pressure-lowering interventions on incidence of dementia and cognitive decline (Peters 2008; McGuinness 2009; van Middelaar 2018). SPRINT-MIND (the **S**ystolic Blood **Pr**essure **Int**ervention Trial: **M**emory and Cognition **in D**ecreased Hypertension sub-study) assessed whether intensive blood pressure treatment (aiming for systolic blood pressure of < 120 mmHg) may lead to a reduction in incident dementia when compared to standard blood pressure treatment (aiming for systolic blood pressure < 140 mmHg). The study reported no significant reduction of incident dementia in the intervention group (hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.67 to 1.04), but did show a reduced risk of incident mild cognitive impairment (HR 0.81, 95% CI 0.69 to 0.95) (Williamson 2019).

High serum cholesterol in midlife has been associated with an increased risk of dementia (Kivipelto 2001). This association is thought to be mediated through two pathways: high serum cholesterol causes atherosclerosis resulting in an increased risk of cardio- and cerebrovascular disease; and high cholesterol levels have been associated with increased amyloid. Both pathways potentially increase the incidence of dementia (Solomon 2007; van Vliet 2009). However, trials of statins have shown no effect on the incidence of dementia (McGuinness 2016).

Trials of other drugs (non-steroidal anti-inflammatory drugs (NSAIDs) (Martin 2008), hormone replacement therapy (HRT) (McCarrey 2015) and vitamin supplements (Winblad 2016; McCleery 2018)) have also shown no effect on the incidence of dementia.

Regarding nutrition, dietary interventions have the potential to prevent many conditions that increase the risk of dementia, such as dyslipidaemia and diabetes. A diet high in long-chain omega-3 polyunsaturated fatty acids has been suggested to protect against dementia due to the vascular and anti-inflammatory properties of these acids (Yehuda 2002; Barberger-Gateau 2007). In addition, a single study suggested positive effects of a Mediterranean diet on cognitive outcomes, although cognitive impairment did not significantly differ between groups and no participants developed dementia (Valls-Pedret 2015).

The association between body mass index (BMI) and dementia seems to be bidirectional, with a high BMI during midlife and a lower BMI in late life associated with an increased risk of dementia (Whitmer 2007; Tolppanen 2014; Yu 2020). This could potentially be attributed to reversed causality since dementia is associated with weight loss as long as 10 years before its onset. Secondly, adiposity leads to insulin resistance and high levels of adipokines and cytokines, all of which have been associated with an increased risk of dementia (Luchsinger 2009).

In addition, type 2 diabetes mellitus has also been associated with cognitive decline and dementia (Cukierman 2005; Lu 2009; Vagelatos 2013). Type 2 diabetes can cause disturbances in brain insulin and insulin-like growth factor signalling mechanisms, potentially promoting molecular, biochemical, and histopathological lesions in Alzheimer's dementia (de la Monte 2008), but these patients often also have other cardiovascular risk factors that could contribute to the incidence of dementia, such as hypertension, high serum cholesterol, and cardiovascular disease (Norton 2014; Leon 2015). It is plausible that the relation between diabetes and dementia is multifactorial. Effective strategies for preventing dementia in these patients has proven to be challenging; a recent Cochrane meta-analysis found no clear evidence that any specific treatment for glycaemic control can prevent or delay cognitive impairment when compared to other treatments (Areosa 2017).

Physical activity might contribute to the prevention of dementia through indirect effects on other modifiable risk factors, such as

obesity, hypertension, high serum cholesterol, and cardiovascular disease. Other potential mechanisms to explain the association between physical activity and dementia could be related to direct neurological effects, such as increased neurogenesis, cerebral blood flow, and brain-derived neurotrophic factor (BDNF) concentrations (Brown 2013; Leckie 2014; Phillips 2014). A recent systematic review did not find evidence of a protective effect of physical activity on the development of dementia (Brasure 2018). However, since protective effects of physical activity might operate largely indirectly, through effects on other risk factors, they may only become apparent over a long period of time.

Cognitive training might reduce the risk of dementia by stimulating cognitive reserve, the ability of the brain to compensate for neurological damage, as well as by protecting against rapid cognitive decline (Stern 2010; Stern 2012). It has been suggested that cognitive stimulation may promote neural plasticity and stimulate the development of compensatory networks in the brain, maintaining cognitive function and potentially masking (or preventing) manifestations of cognitive decline (Grady 2012; Park 2013). To date, the effect of cognitive training in older adults has mainly been studied for the prevention of cognitive decline and there is little evidence for an effect on incident dementia (WHO 2019).

Depression has a well-known association with dementia. There has been much discussion on whether the relationship between depression and dementia is a causal one, or whether depression is a prodromal symptom of the condition. Several longitudinal cohort studies have shown a link between the number of depressive episodes and the onset of dementia, strengthening the hypothesis of a causal relationship (Kessing 2004; Dotson 2010). However, another cohort study found that it was only in the 10 years preceding dementia diagnosis that depression was linked with an increased incidence of dementia, making midlife depression as a risk factor for dementia less likely (Singh-Manoux 2017). Biologically it is plausible that depression increases dementia incidence by affecting stress hormones, neuronal growth factors and hippocampal volume (Sapolsky 1996; Alexopoulos 2003).

Social disengagement has been associated with an increased risk of cognitive decline and dementia (Kuiper 2015). However, as with depression, it is hard to distinguish if the relation between social disengagement and cognitive decline is causal or a prodromal symptom of dementia. A recent systematic review confirmed the presence of this relation in observational evidence, however, did not find a conclusive confirmation on the causality in the three included randomised controlled trials (RCTs) (Kelly 2017).

Tobacco and heavy alcohol usage has been associated with numerous conditions, including cardiovascular disease and depression (Zhou 2014). The association with cognitive decline and dementia (tobacco (Durazzo 2014); alcohol (Langballe 2015; Sachdeva 2016)) could be mediated through these common risk factors or could be caused by the direct neurodegenerative effects of smoking and drinking. To date, the effect of smoking and alcohol cessation interventions on the incidence of cognitive decline and dementia have mainly been studied in observational cohort studies, however, the strong evidence, high population attributable risk, and reproducibility in different settings with different study design suggest a causal relation, either indirect or direct (Lafortune 2016; WHO 2019).

Since sporadic dementia is a multifactorial condition, thought to derive from multiple causes and risk factors, multi-domain interventions may be more effective than those targeting single risk factors. Synergistic interactions between different interventions may occur (Coley 2008; Andrieu 2015; WHO 2019).

This review will focus on randomised controlled trials (RCTs) investigating the effect of risk factor modification within multiple domains simultaneously on cognitive decline and the incidence of dementia. For this review, we defined 'multi-domain interventions' as interventions with more than one component, not including two or more drugs targeting the same therapeutic target (e.g. two antihypertensive medications). Major components of dementia risk factor modification include, but are not limited to, blood pressure lowering drugs, cholesterol lowering drugs, increasing physical activity, and dietary manipulations.

How the intervention might work

To date, no single-domain intervention has convincingly been able to reduce the risk of developing dementia. There are, however, plausible theoretical reasons why multi-domain interventions may have a more beneficial effect on the incidence of dementia. Most common known risk factors for dementia (i.e. hypertension, diabetes, obesity, low education, physical inactivity, depression) are known to cluster together (Livingston 2017). Targeting more than one risk factor for dementia might therefore have additive or even synergistic effects when compared to single-domain interventions (Coley 2008). When aetiology is multifactorial, even a small reduction in several risk factors could drastically decrease dementia risk at the population level (Solomon 2014). It is plausible that cognitive impairment in old age often has mixed aetiologies with shared risk factors, implying that prevention strategies addressing multiple risk factors have the highest likelihood of being effective (Solomon 2014).

Why it is important to do this review

Increased life expectancy in the coming decades will be associated with an increase in both incidence and prevalence of dementia, with a projected global prevalence of 131 million people with dementia by 2050 (Richard 2009; Prince 2015). This projected rise will impose a heavy burden on both social care and healthcare systems.

Currently, no effective medical treatment exists to prevent cognitive decline and dementia. Lack of understanding of the true pathophysiology of dementia limits our ability to develop preventive strategies. Common risk factors are known, however, many of which are potentially modifiable. Many pharmacological and non-pharmacological interventions to prevent long-term complications of modifiable risk factors have been suggested as preventive measures (Richard 2009; Richard 2012; Solomon 2014). Several studies on multi-domain interventions to prevent dementia have been performed in the past decade. With this review, we aimed to assess these studies, to gain more insight in the most promising strategies for both individuals and health systems.

OBJECTIVES

To assess the effects of multi-domain interventions for the prevention of cognitive decline and dementia in older adults, including both unselected populations and populations at increased risk of cognitive decline and dementia.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) with an outcome of cognitive function or incident dementia. We included double-blinded, single-blinded, open and 'prospective, randomised, open, blinded end-point' (PROBE) design studies. We only included studies with a minimum follow-up of 12 months because of the slow onset and progression of symptoms of cognitive decline, and to avoid detecting short-term effects which are not sustainable over time. We only included studies with 400 or more participants, as due to the relatively small potential effect size, the relatively low incidence of the condition under study and the slow progression of symptoms under study, smaller studies can only be considered as proof-of-concept or pilot studies. We included studies published in any language and obtained reliable translations where necessary.

Types of participants

Studies were eligible if they included participants over 50 years of age. We included unselected and high-risk populations; the latter included those with known risk factors for dementia and those with subjective cognitive symptoms or cognitive impairment not fulfilling criteria for a dementia diagnosis.

Types of interventions

We included studies using interventions with more than one component. Components of an intervention could be pharmacological, non-pharmacological or a mixture of both, but could not be solely two or more drugs with the same therapeutic target. The minimum duration of interventions was 12 months. As control conditions we accepted no intervention, (optimised) usual care, placebo treatment or any other type of sham intervention, but not single-domain interventions intended to reduce dementia risk.

Types of outcome measures

Eligible studies had to have a clearly defined outcome measure assessing cognitive function or incidence of dementia. Such outcome measures could be cognitive screening instruments, multi-domain cognitive assessment scales, neuropsychological test batteries, or dementia diagnosis according to any of the validated criteria current at the time of the study.

Primary outcomes

Critical outcomes

- Incidence of dementia or any subtype of dementia
- Cognitive decline, defined by the decline in cognitive functioning measured at two separate occasions with any validated measure, including, but not limited to, screening instruments such as Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), more extensive assessment instruments such as Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and Cambridge Cognition Examination (CAMCOG), more extensive neuropsychological testing such as Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and full neuropsychological examination
- Incidence of mild cognitive impairment (MCI), diagnosed using any definition prevailing at the time of the study, in participants who do not fulfil formal diagnostic criteria for dementia
- Mortality

Secondary outcomes

Important outcomes

- Adverse events, e.g. cardiovascular events such as stroke or myocardial infarction, as defined by the original researchers
- Quality of life, either generic or disease-specific, measured by any validated measure
- Activities of daily living (ADL), measured by any validated questionnaire
- Intervention adherence as reported in the original study (e.g. self-reported, recall questionnaires, attended visits etc.)

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's Specialised Register. ALOIS is maintained by the Information Specialists of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia (prevention and treatment), mild cognitive impairment and cognitive improvement.

The studies are identified from the following.
1. Monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACS.

2. Monthly searches of the trial registers: the WHO International Clinical Trials Registry Platform (which covers ClinicalTrials.gov, ISRCTN, the Chinese Clinical Trials Register, the German Clinical Trials Register, the Iranian Registry of Clinical Trials, and the Netherlands National Trials Register, plus others) and ClinicalTrials.gov

3. Quarterly search of the Cochrane Library's Central Register of Controlled Trials (CENTRAL)

4. Six-monthly searches of a number of grey literature sources from ISI Web of Science Core Collection

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'Methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

We performed additional searches in many of the sources listed above, to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used are described in Appendix 1. The most recent search was carried out on 28 April 2021.

Searching other resources

We reviewed the reference lists of all included trials and of relevant systematic reviews and practice guidelines identified during the screening process. In case of incomplete reports, conference abstracts or trial registrations, we conducted further searches for

connected papers and, if necessary, we contacted authors to obtain missing information.

Data collection and analysis

Selection of studies

We used Cochrane's Screen4Me workflow to identify potential reports of randomised trials in the initial search results. Screen4Me comprises three components: known assessments — a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an RCT or as Not an RCT; the RCT classifier — a machine-learning model that distinguishes RCTs from non-RCTs; and if appropriate, Cochrane Crowd — Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me webpage on the Cochrane Information Specialist's portal. In addition, more detailed information regarding evaluations of the Screen4Me components can be found in the following publications: Thomas 2017; Noel-Storr 2020.

After the Screen4Me process, and a first assessment by the Cochrane Dementia and Cognitive Improvement Group's Information Specialist, two review authors (MH and MH-B) independently screened all remaining titles and abstracts to identify all potentially relevant RCTs. In this phase we were over-inclusive: whenever doubt existed regarding the eligibility of a trial, we included it for full-text assessment. We retrieved the full text of all potentially relevant reports and examined these against our eligibility criteria. Where necessary, we contacted study investigators to clarify study eligibility. We resolved disagreements about study selection by discussion or third party adjudication. We have detailed the study selection process in a PRISMA flow diagram, Figure 1 (Moher 2009).

Figure 1. Study flow diagram.

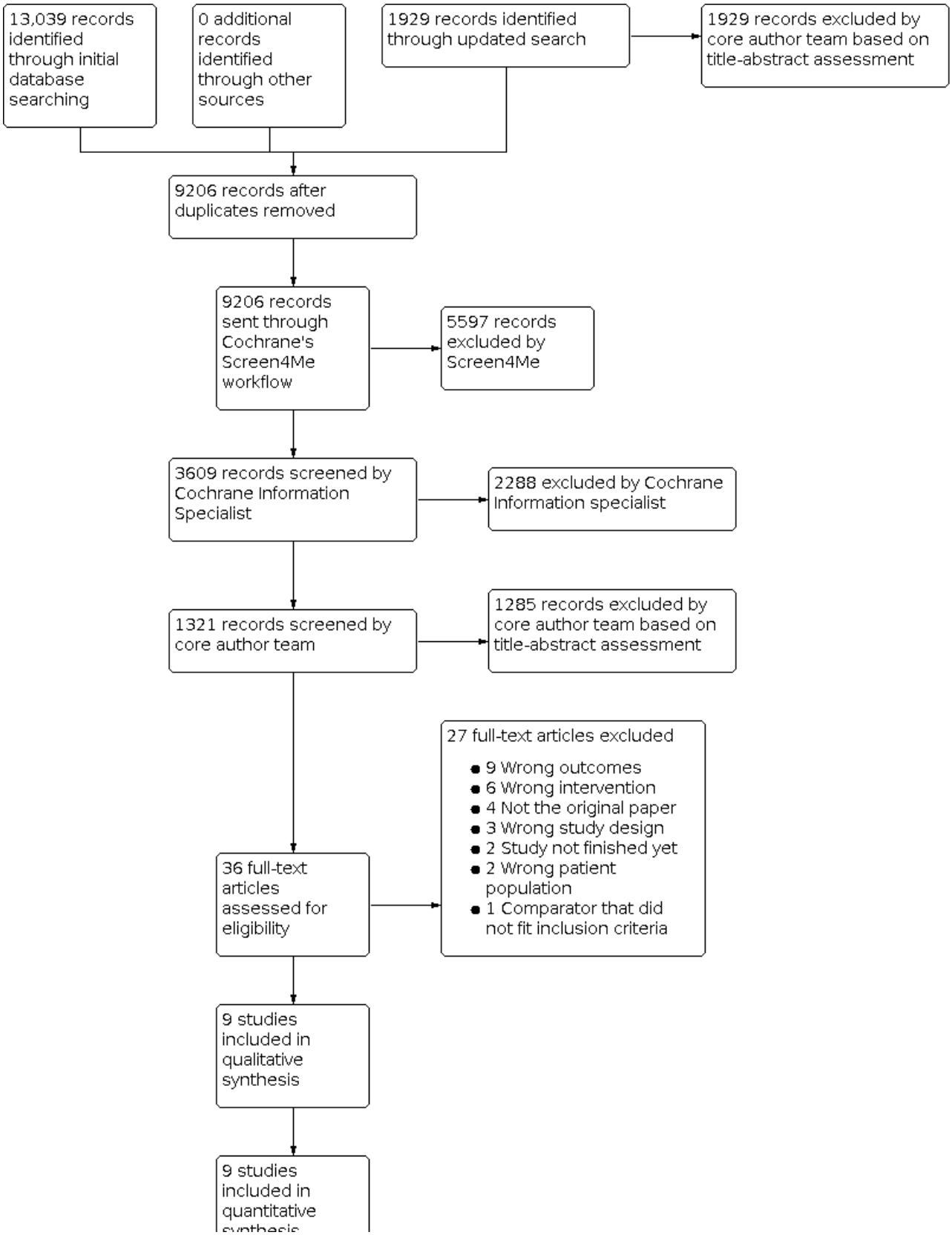
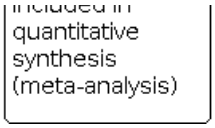


Figure 1. (Continued)



Data extraction and management

Data were extracted using a predefined data extraction sheet that covered: detailed trial characteristics (e.g. setting, outcome measures), design features (e.g. blinding, follow-up procedures), participant characteristics (e.g. age, gender, education, cognitive status, risk factor status), elements of intervention and control (e.g. nature of the intervention, duration, intensity) and trial results. We allowed for comments on trial characteristics within our data extraction form wherever deemed appropriate.

A single review author extracted data on study characteristics, which was checked by a second review author. Two review authors (MH and MH-B) independently extracted outcome data. Outcome data were additionally extracted by a third assessor who was not involved in execution of any of the included studies (MPW, see Acknowledgements). We resolved discrepancies by discussion. All study data were recorded in the prespecified data extraction form and entered into the most recent version of Review Manager software (RevMan Web 2021).

Assessment of risk of bias in included studies

Two review authors (MH and MH-B) independently assessed the internal validity of each included study using the Cochrane risk of bias tool (Higgins 2016). We resolved uncertainties with a third review author (ER). Consistent with the risk of bias tool, we assessed bias in the following domains: sequence generation; allocation concealment; blinding of participants and investigators; incomplete outcome data; and selective reporting of outcomes. We rated all studies as 'low risk', 'high risk' or 'unclear risk' in each of these domains. Additionally, we allowed comments on any other potential risk of bias, not covered in the risk of bias tool, for each included study.

For cluster-randomised trials, we assessed two extra risk of bias domains specifically associated with these designs; recruitment bias, i.e. when individuals are recruited to the trial after the clusters have been randomised, as the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited; and bias caused by baseline imbalances that were not corrected for, as cluster-randomised trials have higher chance of baseline imbalance between the randomised groups, in terms of either the clusters or the individuals. We dealt with any loss of clusters by reporting this in the domain of incomplete outcome data.

Measures of treatment effect

Dichotomous data

For dichotomous data (such as dementia or no dementia) we pooled treatment effect as a risk ratio (RR) with 95% confidence intervals (CIs). For time-to-event outcomes, we used hazard ratios (HRs) and 95% CIs. If treatment effect for a dichotomous outcome was reported as both risk ratios and time-to-event outcome in different studies, we additionally converted the time-to-event outcome to risk ratio, allowing us to pool these studies within our meta-analysis.

Continuous data

For continuous data, we pooled treatment effect as the between-group mean difference (MD) for outcome measures using the same scale or standardised mean difference (SMD) for outcomes measured with different or modified scales. If some scales increase with disease severity whilst others decrease, we multiplied the mean values from one set of studies by −1 to ensure that all the scales pointed in the same direction.

Unit of analysis issues

For each included study, we considered whether groups of individuals were randomised to the same intervention (i.e. cluster randomisation), whether participants underwent multiple observations for the same outcome (i.e. repeated assessments), and whether studies included more than one intervention group (i.e. multi-arm trials). For cluster-randomised trials, we extracted results from analyses that took the effect of clustering into account. For repeated assessments, we tried to report data from mixed models. If a study with repeated assessments did not employ a mixed model or if data from a mixed model were not made available by the study authors, we used the latest outcome assessment from this study. For multi-arm trials, we included all intervention groups that would meet the criteria for inclusion in pairwise comparisons, if they were investigated alone, allowing us to investigate heterogeneity across intervention arms. For these trials, we corrected the weighting of the control group according to the number of included intervention groups from one study, to prevent double-counting participants in the control group.

Dealing with missing data

Missing data in the individual trials may put the study estimates of effects at a high risk of bias and may lower the overall certainty of the evidence according to GRADE (Higgins 2019). We dealt with missing data in our risk of bias assessments. We also conducted sensitivity analyses to explore the effect of excluding studies with high levels of missing data (defined as > 20% of participants included at baseline being missing from the relevant analysis). For all outcomes we carried out analyses on an intention-to-treat (ITT) basis.

Assessment of heterogeneity

We assessed studies that we considered similar enough for data pooling (based on population and outcome) for heterogeneity by visual inspection of forest plots and by using Chi^2 and I^2 statistics for heterogeneity. We regarded statistical heterogeneity to be present when the Chi^2 test was significant at $P = 0.1$; and we defined heterogeneity as low (I^2 up to 40%), moderate (I^2 = 40% to 60%) substantial (I^2 = 60% to 90%) and considerable (I^2 = 90% to 100%).

Assessment of reporting biases

Due to the limited number of included studies, we did not construct a funnel plot to graphically assess reporting biases (see 'Differences between protocol and review').

Data synthesis

We decided on suitability for meta-analysis of each outcome by a qualitative assessment and by assessing statistical heterogeneity of the included studies. If it was not feasible to combine results due to differences in the study characteristics or substantive statistical heterogeneity, we presented results as a narrative summary.

We performed standard pairwise meta-analyses using a random-effects model using Review Manager software for every treatment comparison where the summary analysis would include at least two studies (RevMan Web 2021). We presented the results within the random-effects model as the average treatment effect with 95% CI and with the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We performed two of our predefined subgroup analyses for the effect of multi-domain interventions on cognitive decline:

- Participants with any cognitive impairment versus no cognitive impairment at baseline, defined by:
  - MMSE score.
- Populations at increased risk of dementia, defined by:
  - ApoE4 carrier versus noncarrier.

The other protocol-defined subgroup analyses were not performed due to the prespecified minimum of two trials per subgroup or — for interventions including cognitive training — because no statistical heterogeneity was found (see also 'Differences between protocol and review').

Sensitivity analysis

To investigate the robustness of our findings, we performed the following sensitivity analyses.

- Exclusion of studies of low quality. We defined high-quality studies as those with a low risk of bias across all domains, except for blinding of participants and personnel. We chose not to include bias within this domain for this sensitivity analysis because lifestyle interventions are often difficult to blind, therefore incorporating this domain could potentially induce a discrepancy between pharmacological and lifestyle interventions. We did assess and report whether outcome assessment was blinded; any study in which outcome assessors were not blinded was classified as low quality.
- Exclusion of studies with > 20% missing values not being compensated for by multiple imputation.

We were unable to perform our other prespecified sensitivity analyses as there were no studies available for these analyses (see 'Differences between protocol and review').

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of evidence behind every estimate of treatment effect (Higgins 2019). For each of the critical outcomes of the review, we presented a summary of the amount of data, the magnitude of the effect size and the overall certainty of the evidence in a summary of finding' table, created using GRADEproGDT software (GRADEpro GDT 2020). We defined 'certainty' as the degree of confidence that we can place in the estimates of treatment effects. Rating evidence as high certainty implies that we are confident in the summary estimate of effect, and further research is unlikely to change this. A rating of very low certainty implies that we are very uncertain about the obtained summary estimate of effect. Evidence from RCTs that do not have serious limitations was rated as high certainty. Several factors can lead to downgrading of evidence to 'moderate', 'low', or 'very low'. The degree of downgrading is determined by the seriousness of these factors: risk of bias in included studies; inconsistency; indirectness of evidence; imprecision; and suspected publication bias (Guyatt 2008; Higgins 2019).

RESULTS

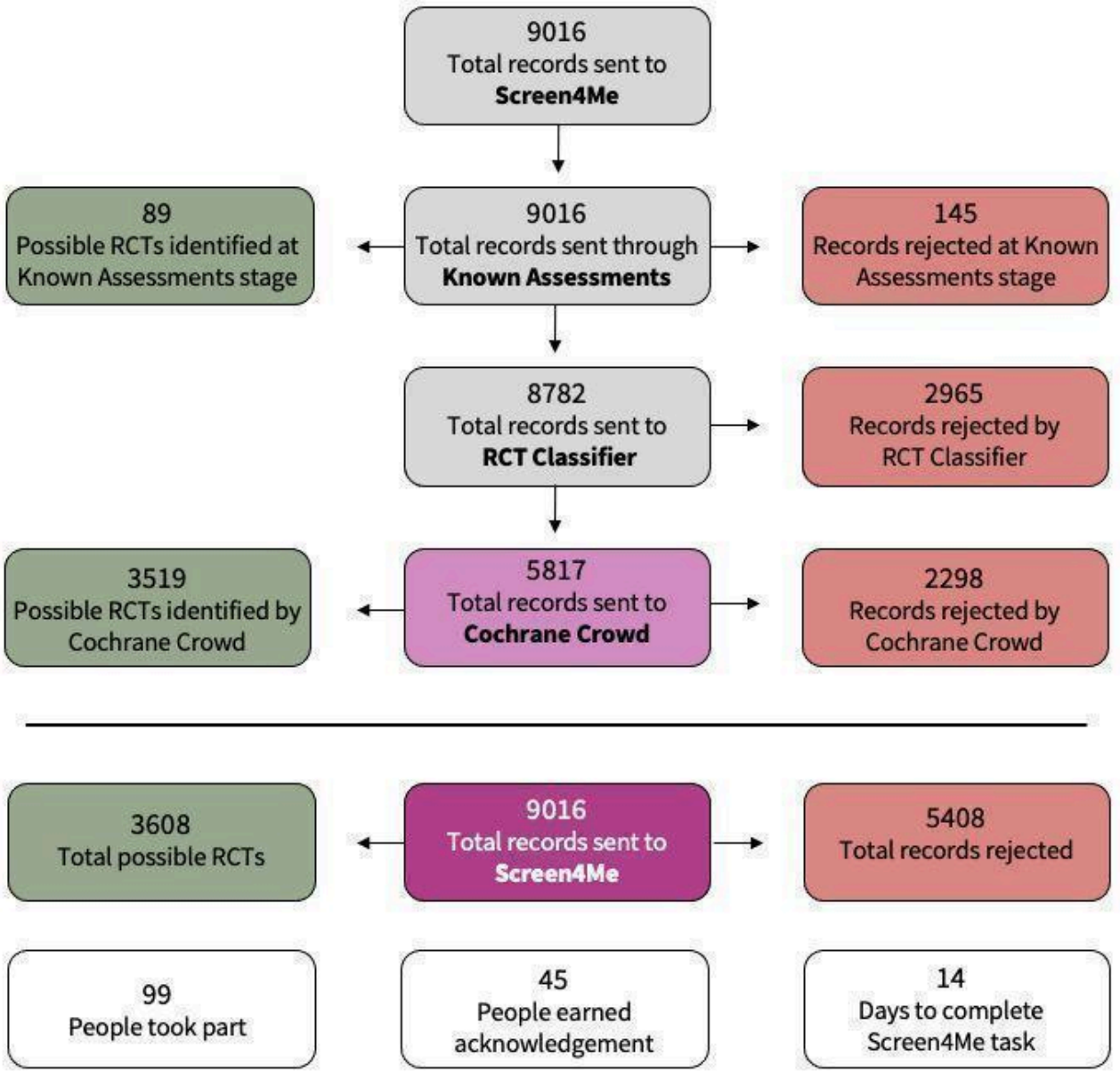
Description of studies

See Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies for a comprehensive overview of included, excluded and ongoing studies. A concise summary of included studies can be found in Table 1.

Results of the search

The initial search identified a total of 13,039 records. These records were screened using Cochrane's Screen4Me workflow to identify potential reports of randomised trials. The results of the Screen4Me assessment process can be seen in Figure 2. This process left 3609 records which were assessed by the Cochrane Dementia Group Information Specialist, who excluded those which were obviously irrelevant, leaving 1321 records for the core author team to assess. Two review authors (MH and MH-B) independently screened the titles and abstracts of these records and excluded 1285 references that were not relevant. Thirty-six full-text articles and protocol papers were assessed for eligibility of which 27 did not meet our inclusion criteria and were excluded. We wrote to two authors of (protocol) papers without published results, but did not receive a response after two contacts. Nine studies are included in this review. We conducted an updated search on 28 April 2021, which identified 1929 additional records but no new studies to include. The selection process is summarised in the PRISMA flow diagram (Figure 1).

Figure 2. Screen4Me figure



Included studies

We included nine studies in this review. These studies are briefly summarised below and described in detail in the Characteristics of included studies table.

Design and setting

All studies used a randomised controlled design. Four studies included multiple intervention arms that fulfilled our inclusion criteria (DR's EXTRA 2010; Lee 2014; MAPT 2017; Li 2018). The other five studies compared a single (multi-domain) intervention to an eligible control group. Three studies were carried out in a community-based setting and six studies were carried out via a healthcare facility.

Participants

A total of 18,452 participants were randomised, with a mean sample size of 2050 participants per study (range 510-5145). The mean age of participants at baseline was 67.8 years. All studies were carried out in community-dwelling participants. Three studies included unselected populations (DR's EXTRA 2010; Lee 2014; preDIVA 2016); one study (FINGER 2015) included participants at increased risk for dementia on a validated multidimensional risk score; one study (MAPT 2017) included participants with memory complaints; one study (Taiwan Health 2020) included (pre)frail participants; and three studies included participants with vascular risk factors (Look AHEAD 2017, diabetes mellitus type-2; Li 2018, hypertension; HATICE 2019, two or more cardiovascular risk factors).

Interventions and comparators

The duration of the interventions varied from 12 months to 10 years. All studies used trained professionals to deliver the intervention. Targeted domains included: diet, physical activity, weight loss, blood pressure control, diabetes management, blood lipids, smoking, alcohol intake, cognitive training, social activities and self-management of risk factors. All nine studies incorporated lifestyle and self-management advice in their intervention. Three studies (FINGER 2015; MAPT 2017; Taiwan Health 2020) also delivered cognitive training to their intervention participants. A comprehensive exercise program was incorporated in four studies (DR's EXTRA 2010; FINGER 2015; MAPT 2017; Taiwan Health 2020). No study used a predefined pharmacological treatment in their intervention strategy.

Most interventions were delivered by trained medical personnel, e.g. nurses, physiotherapists, nutritionists, doctors (DR's EXTRA 2010; Lee 2014; FINGER 2015; preDIVA 2016; MAPT 2017; Li 2018; Taiwan Health 2020); some used trained and blinded study staff (HATICE 2019; Look AHEAD 2017).

As control condition, two studies delivered care as usual via the general practitioner (preDIVA 2016; Li 2018), one study used daily placebo pills and no lifestyle intervention (MAPT 2017), and six studies gave concise health and lifestyle advice (DR's EXTRA 2010; Lee 2014; FINGER 2015; Look AHEAD 2017; HATICE 2019; Taiwan Health 2020).

Outcome measures

Outcomes were assessed after follow-up times ranging from 12 months to 13 years.

Critical outcomes

Incidence of dementia was reported in two included studies (preDIVA 2016; Look AHEAD 2017). Both studies used an independent outcome committee to adjudicate dementia diagnosis in participants with possible dementia.

Cognitive decline was measured in all included studies. Three studies assessed this using a composite score from a neurological test battery (NTB) (FINGER 2015; MAPT 2017; HATICE 2019); six studies used the Mini-Mental State Examination (MMSE, 30-point scale) (DR's EXTRA 2010; Lee 2014; FINGER 2015; preDIVA 2016; MAPT 2017; HATICE 2019); one study used the extended modified Mini Mental Status Examination (3MSE, 100-point scale) (Look AHEAD 2017); two studies used the Montreal Cognitive Assessment (MoCA) (Li 2018; Taiwan Health 2020).

Incidence of mild cognitive impairment *(MCI)* was reported in one study (Look AHEAD 2017) and was adjudicated by an independent outcome committee.

Mortality was reported in four studies (FINGER 2015; preDIVA 2016; Look AHEAD 2017; HATICE 2019).

Important outcomes

Adverse events included combined cardiovascular events (reported by preDIVA 2016; Look AHEAD 2017; MAPT 2017; HATICE 2019), myocardial infarction (reported by FINGER 2015; preDIVA 2016; Look AHEAD 2017; HATICE 2019), and stroke (reported by FINGER 2015; preDIVA 2016; Look AHEAD 2017; HATICE 2019). One study publication (FINGER 2015) reported only stroke and myocardial infarction events for a restricted period of the study, however, the study authors made event rates for the full study duration available to us upon request.

Quality of life was reported by one study (FINGER 2015), operationalised by the RAND-36 questionnaire. We report results for this outcome narratively.

Activities of daily living was measured in five studies (FINGER 2015; preDIVA 2016; MAPT 2017; HATICE 2019; Taiwan Health 2020). It was assessed using the AMC Linear Disability score (ALDS) by one study (preDIVA 2016), Instrumental activities of Daily Living (IADL) by two studies (FINGER 2015; Taiwan Health 2020), strengthened by a hierarchic disability scale (Kingston 2012; FINGER 2015), the Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument (ADCSADLPI) by one study (MAPT 2017), and the late-life function and disability instrument by one study (HATICE 2019). For all scales except one (used by FINGER 2015), a lower score indicates more disability. We multiplied the point estimate of the FINGER 2015 trial with -1 to align the direction of the scales.

Intervention adherence was reported in two studies (preDIVA 2016; MAPT 2017) and was operationalised as the number of times a visit was attended (preDIVA 2016; MAPT 2017), and by counting the number of returned capsules (MAPT 2017).

Excluded studies

We excluded 27 publications, conference abstracts and registered trials (Figure 1) at the full-text stage. Details are given in the Characteristics of excluded studies table, but the main reasons for exclusion were: 10 studies did not report any outcome of interest for this review, six studies had an ineligible intervention, three studies had an ineligible study design, three articles were not the original paper, two studies were not finished yet, two studies studied the wrong patient populations, and one study used an ineligible comparator. We contacted the authors of one excluded study who had described their intention to include cognitive outcomes in their protocol but who did not report cognitive outcomes in their published papers (Araki 2012), but did not get a response. We contacted authors of another study that had no published results but could reasonably be finished at the time of this review (Bai 2017) but did not receive a response. We screened the references of all included studies, but there were no new studies identified.

Risk of bias in included studies

Overall, the quality of included studies was high, with the exception of a high risk of bias in the domain of performance bias (for a detailed analysis of the risk of bias, see Characteristics of included studies). Risk of bias domain ratings are shown per study in Figure 3 and percentage contributions for each domain are shown in Figure 4.

Figure 3.

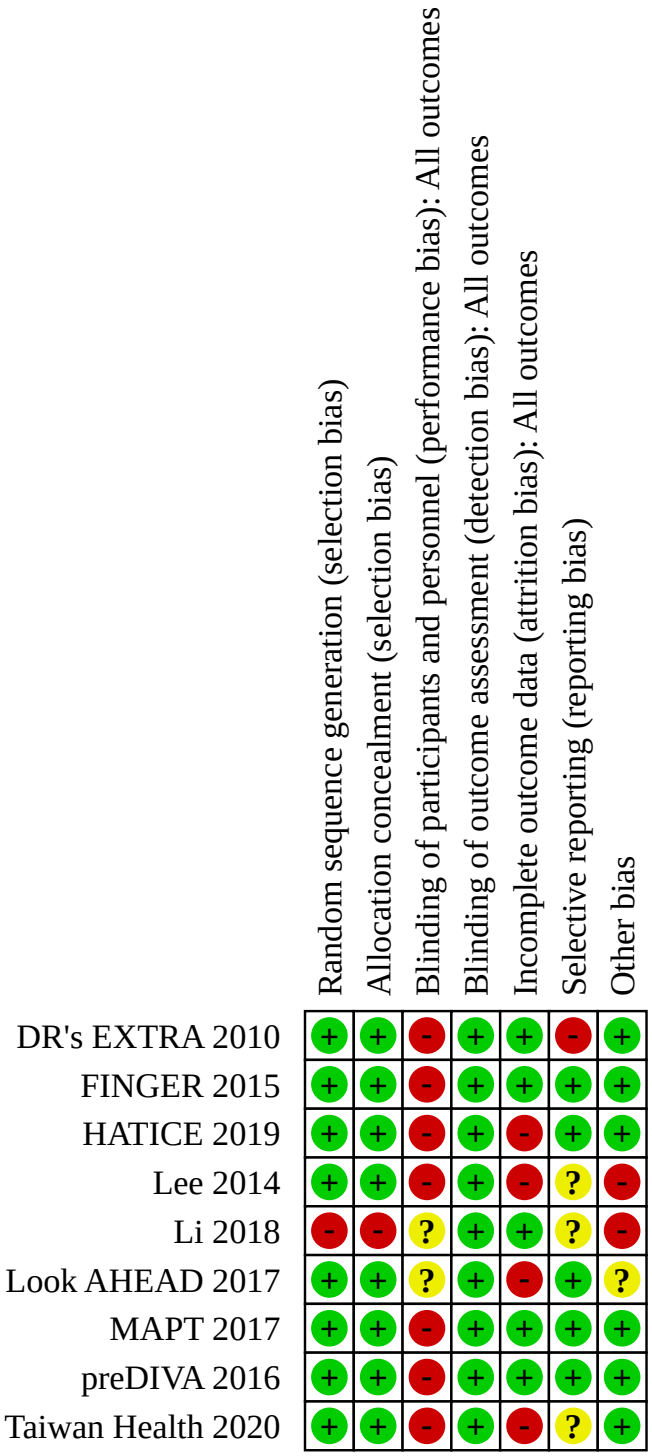
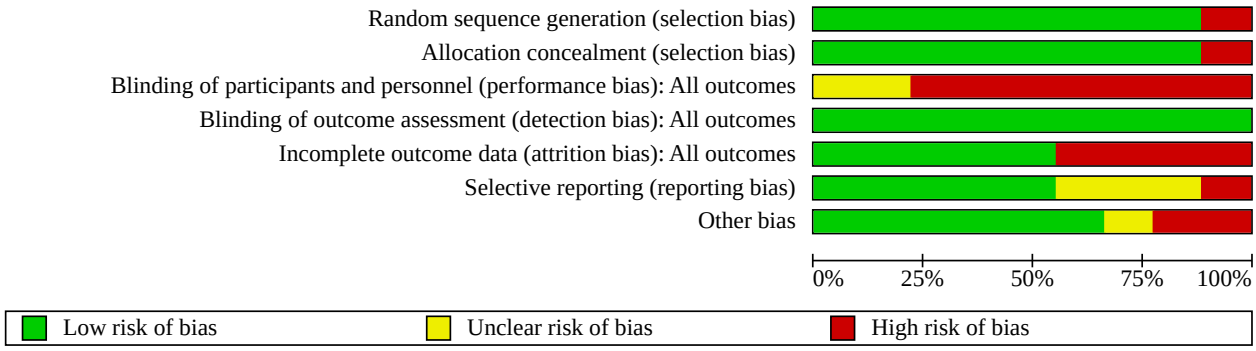


Figure 4.



Allocation

One study was at high risk of selection bias (Li 2018). This trial randomised participants per working district (two districts; workers in Jinduichen area to intervention group, workers in Hancheng area to control group) and allocation of participants could be foreseen. The other included trials were at low risk of selection bias as they used an adequate method of sequence generation and concealed randomisation sequences.

Blinding

We considered seven studies to be at high risk of performance bias as there was no or insufficient blinding of participants and personnel due to the nature of the (lifestyle) intervention under study. We judged two studies to be at unclear risk of performance bias (Look AHEAD 2017; Li 2018) as insufficient details were available on blinding of participants and personnel to make a clear judgement. The risk of detection bias was low in all nine included studies as outcome assessment was conducted independently of the study team and assessors were masked to the treatment allocation of the participants in all studies.

Incomplete outcome data

We considered five studies to be at low risk of attrition bias (DR's EXTRA 2010; FINGER 2015; preDIVA 2016; MAPT 2017; Li 2018). Four studies were at high risk due to incomplete outcome data: two studies had a very high loss to follow-up during the study (Taiwan Health 2020, 25% in intervention group, 30% in control group; Look AHEAD 2017, 26% of all participants); one study (Lee 2014) randomised participants and asked for consent after randomisation, making it unclear whether participants died before or after randomisation, and more than half of the participants dropped out during the intervention and were not retrieved for final assessment; one study (HATICE 2019) had differential drop-out in the intervention and control group for the NTB and MMSE-score (intervention versus control 81% versus 87% and 86% versus 91%, respectively).

Selective reporting

We assessed one study to be at high risk of selective reporting: DR's EXTRA 2010 obtained a score on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) NTB for all participants, but did not report on individual tests nor total scores. We considered three trials to be at an unclear risk of selective reporting bias, as these studies did not publish a protocol (Lee 2014; Li 2018; Taiwan Health 2020), did not register their trial in a trial register (Lee 2014; Li 2018), or only identified primary but not secondary outcomes in their trial registration (Taiwan Health 2020). One study (FINGER 2015) obtained but did not publish the effect of their intervention on the MMSE score, however the authors of this study made their findings available to us upon request.

Other potential sources of bias

We identified other potential sources of bias in three included studies. One study (Lee 2014) was at high risk of bias due to poor statistical analyses: the unit of analysis was the cluster, whereas the unit of analysis should have been the individual, taking into account a cluster effect by for example, random-effects models; for the outcome (MMSE) only single and not multiple imputation was used, thereby not taking random variation into account for the confidence interval; the reported effect sizes could not be fully interpreted as it was unclear for the control group what the follow-up MMSE was. Another study (Li 2018) was at high risk of bias due to unclear reporting of statistical analyses (one-way ANOVA for two group comparison). We assessed one study (Look AHEAD 2017) as being at unclear risk of bias as the study was partially funded by commercial funding sources but did not explicitly state the exact role of their funding sources.

Effects of interventions

See: **Summary of findings 1** Multi-domain interventions compared to usual care/placebo for the prevention of dementia and cognitive decline

We refer to our Summary of findings 1 for an overview of our main outcomes.

Critical outcomes

Incidence of dementia. Two studies (preDIVA 2016; Look AHEAD 2017) provided high-certainty evidence on dementia incidence. Dementia occurred in 155 of 3771 participants (4%) receiving a multi-domain intervention and in 146 of 3485 participants (4%) in the control group. There was no evidence of a difference in the incidence of dementia between the multi-domain and the control group (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.76 to 1.18; 2 studies; 7256 participants; high-certainty evidence; Analysis 1.2). One study (preDIVA 2016) also reported dementia incidence as a time-to-event outcome (hazard ratio (HR) 0.92, 95% CI 0.71 to 1.19). Sensitivity analysis excluding studies with > 20% missing values or

exclusion of studies of low quality did not affect the outcome of our meta-analysis (for both analyses RR 0.93, 95% CI 0.73 to 1.20; 1 study; 3454 participants; Analysis 1.4).

Incidence of MCI. One study reported on incidence of MCI (Look AHEAD 2017). There was probably no difference in MCI incidence between the intervention group (MCI occurred in 122 of 1918 participants (6%)) and the control group (MCI occurred in 124 of 1884 participants (7%); RR 0.97, 95% CI 0.76 to 1.23; 1 study; 3802 participants, moderate-certainty evidence; Analysis 2.1). We downgraded the evidence to moderate quality due to indirectness as the study participants all had a history of diabetes type 2.

Cognitive decline: *Composite score (NTB)*. Three studies (FINGER 2015; MAPT 2017; HATICE 2019) provided evidence on cognitive functioning measured with a composite score of cognitive tests (NTB). There was a small difference in composite Z-score in favour of the multi-domain intervention group (mean difference (MD) 0.03, 95% CI 0.01 to 0.06; 3 studies (4 intervention arms); 4617 participants; high-certainty evidence; Analysis 3.1). Sensitivity analysis excluding studies with high risk of bias in one or more domains resulted in a slightly larger effect on this outcome (MD 0.06, 95% CI 0.01 to 0.10; 2 studies; 2334 participants;Analysis 3.4 (3 intervention arms)).

Cognitive decline: *MMSE score*. Six studies (DR's EXTRA 2010; Lee 2014; FINGER 2015; preDIVA 2016; MAPT 2017; HATICE 2019) provided evidence that there was no statistically significant difference in cognitive functioning measured with the MMSE between the multi-domain intervention and control group (MD 0.02 point, 95% CI -0.06 to 0.09; 6 studies (11 intervention arms); 8697participants; moderate-certainty evidence; Analysis 3.2). We downgraded the evidence for indirectness as the MMSE is a screening tool that has not formally been developed to quantify cognitive decline over time. Sensitivity analysis excluding studies with high risk of bias in one or more domains did not affect the effects on MMSE (MD 0.03 point, 95% CI -0.06 to 0.13; 3 studies (4 intervention arms; 5158 participants; Analysis 3.5)), nor did exclusion of studies with > 20% missing values (MD 0.01 point, 95% CI -0.07 to 0.08; 5 studies (7 intervention arms)). One study (Look AHEAD 2017) was not included in this meta-analysis as it used a modified version of the MMSE (3MSE) but did also not observe a difference in cognitive decline measured with the 3MSE (MD 0.06 point, 95% CI -0.31 to 0.44).

Cognitive decline: *MoCA score*. Two studies (Li 2018; Taiwan Health 2020) accounting for 1554 participants provided very low-certainty evidence that cognitive functioning measured with the MoCA might improve slightly in participants receiving a multi-domain intervention compared to the control group (Analysis 3.3). We downgraded the evidence for very serious risk of bias (Li; no allocation concealment, no individual randomisation, no clear description of source population, unclear statistics), inconsistency ($Chi^2 = 177.80$, df = 2 ($P < 0.00001$); $I^2 = 99\%$) and indirectness as the MoCA is a screening tool that has not formally been developed to quantify cognitive decline over time.

Mortality. Four studies provided evidence on mortality (FINGER 2015; preDIVA 2016; Look AHEAD 2017; HATICE 2019). 577 of 5924 participants (10%) receiving a multi-domain intervention died during the follow-up period, versus 570 of 5563 participants (10%) in the control group. There was no evidence of a difference in mortality between the multi-domain and control group (RR 0.93, 95% CI 0.84 to 1.04; 4 studies; 11,487 participants; hi gh-certainty evidence; Analysis 4.1). Two studies (preDIVA 2016; Look AHEAD 2017) contributed most of the weight of this meta-analysis due to a high cumulative mortality rate, as these studies had a very long follow-up and relatively old population compared to the other studies. Sensitivity analysis excluding studies with high risk of bias in one or more domain(s) did not influence the outcome (RR 1.00, 95% CI 0.86 to 1.15; 2 studies; 4779 participants; Analysis 4.5).

Important outcomes

Adverse events: *Cardiovascular disease.* Four studies (preDIVA 2016; Look AHEAD 2017; MAPT 2017; HATICE 2019) reported on incidence of cardiovascular events. There was no evidence of a difference in cardiovascular event incidence between the multi-domain and control group (RR 1.04, 95% CI 0.93 to 1.15; 4 studies (5 intervention arms); 11,879 participants; high-certainty evidence; Analysis 4.2).

Adverse events: *Myocardial infarction.* Four studies (FINGER 2015; preDIVA 2016; Look AHEAD 2017; HATICE 2019) reported on incidence of myocardial infarction. There was no evidence of a significant effect on myocardial infarction incidence between the multi-domain and control group (RR 0.89, 95% CI 0.75 to 1.06; 4 studies; 11,965 participants; high-certainty evidence; Analysis 4.3). Two studies (preDIVA 2016; Look AHEAD 2017) contributed most of the weight of this meta-analysis due to a high cumulative incidence of myocardial infarction, as these studies had very long follow-up (6 and 10 years, respectively) and relatively old populations (mean age at randomisation 74.5 and 69.6 years, respectively).

Adverse events: *Stroke.* Three studies (FINGER 2015; preDIVA 2016; HATICE 2019) reported on incidence of stroke. There was no evidence of a difference in stroke incidence between the multi-domain and control group (RR 0.75, 95% CI 0.38 to 1.49, three studies, 6822 participants, high-certainty evidence; Analysis 4.4).

Quality of life. Only one study reported on quality of life (FINGER 2015). In this study, mean quality of life scores decreased in all domains in both the intervention and control group over 24 months without any significant difference (mean change on the RAND-36 scale in intervention/control: physical activity -2.3/-4.0, role physical -17/-4.7, role mental -0.1/-1.7, vitality -0.3/-0.9, -0.6/-0.9, social function -0.8/-1.2, bodily pain -2.4/-2.1) except for the domain of general health which decreased in the control group and increased in the intervention group (mean change on RAND-36 scale in intervention/control: 1.5/-1.6, $P < 0.001$).

Activities of daily living (ADL). Five studies (FINGER 2015; preDIVA 2016; MAPT 2017; HATICE 2019; Taiwan Health 2020) provided high-certainty evidence that there was no effect of a multi-domain intervention on ADL (standardised mean difference (SMD) -0.00 95% CI -0.05 to 0.04; 5 studies (6 intervention arms); 7795 participants; high-certainty evidence; Analysis 5.1).

Intervention adherence. Two studies (preDIVA 2016; MAPT 2017) reported on adherence to the intervention. There was low-certainty evidence that participants in the control group were more likely to be adherent to the study conditions (risk difference -26%, 95% CI -37% to -14%; 2 studies (3 intervention arms); 4557 participants; Analysis 6.1). We downgraded the evidence two points for severe inconsistency ($Chi^2 = 24.07$, $P < 0.00001$, $I^2 = 92\%$).

Subgroup analyses

Participants at increased risk of dementia and cognitive decline: *Effect by ApoE4 genotype* **.**
Two studies (FINGER 2015; MAPT 2017) reported their results stratified by ApoE4 genotype (carrier or noncarrier) accounting for a total of 585 carriers of ApoE4 and 1458 noncarriers of ApoE4. There was high-certainty evidence that cognitive functioning measured by a NTB Z-score slightly improved in ApoE4 carriers receiving a multi-domain intervention (MD 0.14, 95% CI 0.04 to 0.25) but not in noncarriers (MD 0.04, 95% CI -0.02 to 0.10, P for interaction 0.09).

Participants at increased risk of dementia and cognitive decline: *Baseline* Cardiovascular Risk Factors, Aging, and Incidence of Dementia (*CAIDE) > 6 points* **.**
Two studies (FINGER 2015; MAPT 2017) reported results for participants with a baseline CAIDE risk score of > 6 points. There was high-certainty evidence that receiving a multi-domain intervention slightly improved cognition measured with a NTB Z-score, though this effect was not statistically significant (MD 0.07, 95% CI -0.00 to 0 0.15, 2157 participants; Analysis 7.3). Because only one study (MAPT 2017) reported on participants with a CAIDE ≤ 6, we could not perform a pooled analysis for this group, nor test for subgroup differences.

Cognitive impairment at baseline: *Effect by MMSE-score at baseline.*
Two studies (FINGER 2015; MAPT 2017) reported their results stratified by baseline cognitive status, based on the baseline MMSE score (MAPT < 30 points, FINGER < 26 points). There was high-certainty evidence that receiving a multi-domain intervention slightly improved cognition measured by a NTB Z-score in participants with a low baseline MMSE (MD 0.06, 95% CI 0.01 to 0.11; 1414 participants) but not in participants with a high baseline MMSE score (MD 0.01, 95% CI -0.01 to 0.04; 917 participants) but the interaction was not statistically significant (P = 0.12).

DISCUSSION

Summary of main results

The objective of this review was to assess the effect of multi-domain interventions for the prevention of cognitive decline and dementia. We included two studies assessing the effect on dementia incidence and found no evidence of an intervention effect. Assessment of cognitive functioning differed greatly across studies and ranged from complete neuropsychological assessments to screening tests (Mini-Mental State Examination (MMSE), modifiedMini-Mental State Examination (3MSE), Montreal Cognitive Assessment (MoCA)). Cognitive functioning measured with a neuropsychological test battery (NTB) and with the MoCA improved slightly in participants receiving a multi-domain intervention, but the certainty of evidence for the MoCA was very low. There was no evidence of improved cognition measured with the MMSE.

Overall completeness and applicability of evidence

This review provides some evidence towards the answer of our review questions, however, the studies identified were not sufficient to fully answer all of the objectives of the review. Overall, only two studies looked at the effect of multi-domain interventions on dementia incidence (preDIVA 2016; Look AHEAD 2017). This lack of evidence may reflect the methodological challenges of dementia prevention trials, as these trials require long-term surveillance of participants and large sample sizes due to the slow progression and low incidence of the condition under study (Richard 2012). All nine included studies reported on change in cognitive performance but the method of assessment differed greatly. Data on cognitive performance are often difficult to interpret with different results depending on the different measures used, hence, determining the clinical importance of the observed changes is challenging. Moreover, many of the included studies incorporated some form of cognitive training in their multi-domain intervention. Though most studies made an explicit effort to separate the intervention component from the outcome measure, it remains difficult to determine how much of the observed effect is true improvement of cognition due to the intervention, which could eventually translate into the prevention of cognitive decline, and how much may stem from an acquired learning effect due to the cognitive training.

Another challenge was the differing components and intensity of the multi-domain interventions. Although all studies were carried out in settings with a high quality of care, some studies were of lower intensity or targeted potentially less effective domains than others. For our meta-analysis, we considered all interventions as comparable. Therefore, we cannot make any recommendations on the potency of individual strategies or domains. Additionally, the duration of included studies ranged from 1 to 10 years. We did not account for these varying intervention times in our analyses, as we did not expect a strong dose-response relation between multi-domain interventions and cognitive functioning or dementia incidence. However, a recent systematic review investigating interventions targeting cardiovascular risk factors found that treatment effects were consistently higher in short-term studies than long-term studies (Beishuizen 2016). It is possible that in these short-term studies more often an effect of the intervention is detected that may not be sustainable over time. However, this was beyond the scope of this review.

Most included studies (DR's EXTRA 2010; FINGER 2015; preDIVA 2016; Look AHEAD 2017; MAPT 2017; HATICE 2019; Taiwan Health 2020) were population-based studies with cognitive functioning or dementia as a primary outcome, making the results of this review especially generalisable for the general population. Only two studies addressed dementia or changes in cognition as a secondary outcome (Look AHEAD 2017, dementia; HATICE 2019, cognitive functioning). It was not possible to thoroughly investigate the interaction of the intervention with increased risk in participants because we could not pool the results of these studies, as they often used a different operationalisation or cut-off value to determine the presence of a risk factor that was not similar enough. Similarly, increased risk of dementia is not a standardised concept; definitions range from cognitive scoring deviations and individual risk factors to comprehensive validated risk scores.

It should be noted that all of our included studies were carried out in middle- or high-income countries. As all interventions were compared against at least usual care, it is plausible that the differences between the intervention and control groups were mitigated by the high level of standard vascular care in these countries. Because there were no trials performed in a setting with low standards of vascular care to include, establishing this contrast was not possible.

We have tried hard to obtain data for studies that have not been fully published, or for which there have been delays in publication,

nevertheless the results of some studies are still not in the public domain and there could be publication bias.

We identified several ongoing studies of multi-domain interventions. The designs and content of these studies are largely overlapping with the evidence described in this review, and it will be interesting to update our analyses once these studies are finished and published. Based on the current body of evidence, we identified several important learning points and directions for future trials to consider (see Implications for research).

Quality of the evidence

This review included nine randomised controlled trials (RCTs) (18,452 participants) of overall high methodological quality. None of the studies had adequate blinding of participants or personnel during the study due to the nature of the intervention, but outcome assessment was adequately blinded in all included studies. All analyses were by intention-to-treat.

The evidence on the effects of multi-domain interventions on prevention of dementia incidence was of high certainty. As the GRADE appraisal of included studies was generally high, this would mean that we can be quite confident of these results when applied in unselected populations. However, we reckon that trial populations are generally different from the general population. The effect on mild cognitive impairment (MCI) incidence was only investigated in one RCT carried out in a diabetes population, therefore we downgraded this evidence to moderate certainty for indirectness. Cognitive decline had a very varied operationalisation, ranging from full neuropsychological testing to simple screening tests such as the MoCA and corresponding certainty levels varying from high to very low.

On the basis of three RCTs there was high-certainty evidence that multi-domain interventions could be very modestly beneficial for cognitive functioning measured with an NTB. Evidence for change in cognition measured with the MMSE was downgraded for indirectness as this scoring is primarily validated as a screening tool and not developed to detect changes over time, nor is there a clear definition how these changes over time translate exactly into cognitive impairment. Cognitive decline measured with the MoCA was downgraded for this same reason and additionally downgraded for inconsistency due to large observed heterogeneity and downgraded for very serious risk of bias. (Li 2018 was at very high risk of selection and allocation bias as it performed no individual randomisation nor was allocation concealed or random; the applied statistics were very unclear and reported results were open to diverging interpretations. Taiwan Health 2020 was at high risk of attrition bias as there was high (potentially differential) drop-out in both the intervention and control group up of to 30% of participants).

Overall, the certainty of evidence was high to moderate according to GRADE criteria for most of our critical outcomes. Especially for cognitive decline, the clinical translation of scoring results to cognitive decline is challenging and requires some precaution. Therefore, we have moderate confidence in the summary estimates of effects reported here.

Potential biases in the review process

We believe that in adhering to the recommended Cochrane search and review methods, we have identified all data of interest to the review question. We did not detect publication bias but cannot formally rule this out as we identified two protocol papers without published results, but did not receive a response from the authors on whether these studies were carried out and/or published. We could not assess publication bias in funnel plot evaluations because of the limited number of identified studies.

For this review, we made an a-priori decision to operate a threshold for inclusion in this review for the minimum number of included participants (> 400). Inevitably, this has led to exclusion of a substantial proportion from the published literature, however, these small studies, that can generally be considered as proof-of-concept trials, are often subject to small-study effects, and including them would have introduced bias (Hopewell 2009). Moreover, these smaller studies will generally be underpowered to detect an effect or demonstrate the absence of an effect as the expected effect size of multi-domain intervention studies on the condition under study is small. Similarly, we determined a threshold for a minimum intervention and follow-up duration of 12 months, because the slow onset and progression of cognitive decline and dementia. Conceivably, studies with a shorter duration are likely to detect short-term effects that are not sustainable over time (Beishuizen 2016).

For multi-arm trials, we included each pair-wise comparison separately, but with shared control groups divided evenly among the comparisons as suggested by the Cochrane Handbook. We opted for this approach as it allowed us to investigate heterogeneity across intervention arms better. However, as the resulting comparisons remain correlated, this method only partially overcomes the unit-of-analysis error, and ideally we would have accounted for the correlation between correlated comparisons from the same study in the analysis.

Another encountered unit-of-analysis issue was the reporting of repeated measurements of several studies. Several authors have made the results of their mixed-model analyses available to us upon request (preDIVA 2016; HATICE 2019), however, for some studies we could not obtain these data and had to use the longest follow-up measurement (FINGER 2015; Taiwan Health 2020). This may have had small effects on the reported effect sizes and corresponding confidence intervals of these analyses (NTB, FINGER 2015; ADL, Taiwan Health 2020).

Agreements and disagreements with other studies or reviews

Much of the existing evidence to support risk factor modification to prevent dementia or cognitive decline stems from epidemiological/observational studies. Reviews of these observational data have suggested that up to 40% of dementia might be prevented through modifiable risk factors (Barnes 2011; Norton 2014; Livingston 2020), but a large gap exists between these findings of observational studies and inconclusive and null-findings of clinical trials (Coley 2008; Andrieu 2015). In addition, if 40% of all dementia is related to potentially modifiable risk factors, this does not translate in 40% of dementia being potentially preventable, since eradication of all risk factors is not realistic. Our findings are congruent with previous papers that have reported on multi-domain intervention trials (Andrieu 2015; Toman 2018; Eggink 2019; Rosenberg 2020). The systematic review by Toman 2018 indicated that risk factor modification may be beneficial to maintain cognitive health based on cross-sectional and cohort studies but could not affirm causality

based on RCTs. Another recent review (Eggink 2019) reported no effect of single-domain intervention trials on dementia. The World Healthe Organization (WHO) guideline on risk reduction of cognitive decline and dementia also reported insufficient or little evidence for the recommendation of single-domain intervention,s but stated that physical activity and a Mediterranean-like diet may be recommended to reduce this risk of cognitive decline and dementia (WHO 2019). These recommendations can be argued, since the evidence from intervention studies is debatable. However, it should be noted that most of these single-domain interventions have beneficial effects over and above prevention of cognitive decline and dementia and may still be warranted.

The review by Rosenberg 2020 concluded that targeting at-risk individuals (as opposed to an unselected population) is likely the most feasible strategy for multi-domain prevention trials as cognitive benefits were suggested in subpopulations of participants with increased risk of dementia (preDIVA 2016; MAPT 2017), and in one trial performed in participants at increased risk of dementia (FINGER 2015). In this review, we observed a similar interaction for participants at increased risk of cognitive decline and dementia defined by ApoE4 status, but the interaction for baseline cognitive status (defined by MMSE score) was not statistically significant. The definition of participants at risk is crucial, as the window of opportunity for prevention may have passed for some populations but may be too early for sustainable changes in others (see also: Implications for research).

AUTHORS' CONCLUSIONS

Implications for practice

We found no convincing evidence that multi-domain interventions can prevent incident dementia based on two trials. There was high-certainty evidence for a small effect on cognitive functioning (assessed by a neurological test battery (NTB)) in favour of multi-domain interventions, though this effect was not consistent with the: Mini-Mental State Examination (MMSE) and was only observed in studies offering some form of cognitive training to their intervention participants, making it difficult to rule out a potential learning effect of cognitive testing in the intervention group, rather than a true effect on cognitive decline due the multi-domain intervention itself. Evidence on the effect of multi-domain interventions on the MMSE was downgraded one point for indirectness, as the MMSE is a screening tool that is not formally developed to detect changes over time and might not be suitable to detect subtle changes in individuals, that may be relevant on a populations scale (Hensel 2007). There was high-certainty evidence for an interaction of ApoE4 status on cognitive functioning measured with a NTB, but no statistical significant evidence for an interaction of baseline cognitive status (defined by the MMSE) on cognitive functioning measured by an NTB (low baseline MMSE group MD 0.06, 95% CI 0.01 to 0.11, high baseline MMSE group MD 0.01, 95% CI -0.01 to 0.04, P for interaction 0.12) or on cognitive functioning measured by an NTB for participants with a Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score > 6 (MD 0.07, 95%CI 0.00-0.15).

Fear of developing dementia is common among older adults, and there is increasing demand for interventions to prevent cognitive decline. Despite the absence of clear evidence of an effect of multi-domain interventions on incident dementia and cognitive decline, there is considerable evidence from randomised studies that optimising cardiovascular risk factors can reduce the risk of cardiovascular disease (Cooper 2000; Ford 2007; Bailey 2016). In spite of the absence of a clear effect, point estimates in our review suggest a potential modest effect on cognitive functioning. Such a small effect may eventually be relevant, since even a very modest effect can have preventive implications when implemented in a population-based setting (Rose 2001) and when proven sustainable over longer periods of time.

Beside efficacy of the intervention, it will be important to investigate the implementation, considering acceptability, adoption, scalability and sustainability of multi-domain interventions in actual community settings (Peters 2013). As many components of the multi-domain interventions comprise management of cardiovascular risk factors, it would be sensible to aim for implementation of these interventions in already established prevention programmes for these risk factors. A multidisciplinary approach should be encouraged to maximally optimise the synergistic nature of multi-domain interventions, but should preferably remain simple without compromising too much on scalability and implementation options for low- and middle-income countries.

Implications for research

The complex nature of cognitive decline and dementia translates into the need to identify risk profiles in which there is opportunity for prevention. The use of biomarkers could be an appropriate approach to select individuals at increased risk of dementia for clinical trials, but this is hardly feasible for implementation in large-scale prevention strategies and may not select the correct population for multi-domain prevention studies, as the increased risk indicated by biomarkers doe not necessarily indicate a population with potential benefit from a multi-domain intervention. Participants at risk could be identified by using dementia risk scores. Several prediction models were developed to calculate individual dementia risk, based on established and readily available risk factors for dementia (CAIDE, Kivipelto 2006; late-life dementia risk index, Barnes 2009; LIBRA, Schiepers 2018). A common limitation of these risk scores is that they often comprise both modifiable and non-modifiable risk factors. The latter may improve predictive accuracy but are not subjective to change and therefore potentially overestimates the opportunity for prevention. Lastly, the presence of early signs of cognitive decline could be used to identify populations at increased risk. However, this will include people at an early stage of the disease, leading to a different population, which will not entail primary prevention anymore.

Subsequently, the timing of the intervention is crucial, as an intervention too late will yield very limited efficacy and may have even passed the window for prevention but an intervention too early will require too long adherence and follow-up to be realistic. The optimal age for prevention of cognitive decline and dementia is still unknown, but is presumably in midlife and not in late life (Richard 2012). Moreover, for several risk factors the association with dementia and cognitive decline is modified by age and the optimal timing for an intervention may differ (Legdeur 2018). For some risk factors, such as hypertension and obesity, increasing values are associated with dementia in midlife but the opposite has been reported for late-life, therefore the intervention should be well-timed (Kivipelto 2005; Tolppanen 2012).

The difference in the components targeted and the intensity with which they are targeted should also carefully be considered. For this review, we considered 'multi-domain interventions' as an umbrella term for a wide range of combinations of targeted domains related to dementia risk. Therefore, recommendations on the most effective components of multi-domain interventions cannot be made. The intensity of the intervention could additionally have effect on the adherence and ultimately efficacy of the intervention. A study on determinants of adherence in two of the included studies (FINGER 2015; MAPT 2017) found that adherence decreased with increasing intervention complexity and intensity, underlining the delicate balance between over- and under-burdening of participants (Coley 2019). Future research should focus on exploring these knowledge gaps, for example by using multi-arm intervention designs to scrutinise the potency of different components and intensity regimens.

Another relevant timing is that of the outcome assessment. The largest effect of the intervention can probably be expected in relatively young study populations, however, follow-up would have to be decades to identify sufficient dementia cases. The choice of a fitting outcome measurement is another challenge. A preferred outcome should be easy to interpret and clinically relevant, such as a clinical diagnosis of dementia according to the locally prevailing guidelines, however, as the largest effect of the intervention can probably be expected in relatively young study populations, long follow-up times will be needed which calls for long-term vision of both researchers and funding sources. Determining decline in cognition as an outcome could be a suitable alternative but assessment is heterogeneous and determining a clinically relevant change is not straightforward. The more sensitive composite scores yield promising potential to capture intervention effects, yet, future studies should aim to determine and provide cut-off values for these scores that are clinically relevant for participants and carers — which in the end needs confirmation with long-term effects that are meaningful for patients. Moreover, neuropsychological tests often have a ceiling effect in younger populations with no cognitive complaints, making it problematic to detect changes in these populations.

Lastly, improvement in the control group is not uncommon in multi-domain intervention studies (FINGER 2015; preDIVA 2016). This effect could partially be explained by the baseline measurements that result in awareness and in some cases treatment of vascular risk factors (such as hypertension or dyslipidaemia) because not revealing these results to participants would be unethical. Similarly, behaviour of participants is likely to change when participating in a trial, independent of treatment allocation, as a reaction to awareness of the study (Hawthorne effect). Both these mechanisms could mask the true effect of the intervention, potentially leading to type-II errors. Similarly, most countries that have conducted RCTs to investigate the effect of multi-domain interventions had a high-level standard of usual (vascular) care, potentially mitigating the contrast between the intervention and control group.

Overall, the design and execution of cognitive decline and dementia prevention trials may be complicated, but increasing experience from past and ongoing trials will allow for careful design of future trials. These trials will need to be large with preferably long follow-up times, clinically-relevant outcome measures and could potentially be expanded to relevant risk populations. Furthermore, with a projected increase of dementia incidence and a high prevalence of dementia risk factors in especially low- and middle-income countries (LMIC), targeting these populations could be very promising, creating a need for more population-based multi-domain intervention trials in these countries (Livingston 2017; Mukadam 2019). Finally, implementation research on multi-domain intervention studies for the prevention of cognitive decline and dementia is warranted, to ensure effective implementation of these interventions on a large scale is feasible and leads to sustained adoption and sustained effects over time.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

DR's EXTRA 2010

Study characteristics	
Methods	**Study design** RCT **Total study duration** 2003-2010 **Duration of follow-up** 2 years (for cognition)
Participants	**Population description** Random sample from national population register *Risk population description (if applicable)* Not applicable **Baseline age** Mean 65.9 years **Setting of study** Study centres **Inclusion criteria** Living in Kuopio (Finland), 55-74 years (in 2002) **Exclusion criteria** Health conditions that impair safe exercise training, malignancies and conditions preventing co-operation e.g. dementia **Participants randomised** *Total*: 1410 (not all study arms were eligible for inclusion in this review) *Intervention*: Group 1: 234, group 2: 234 *Control*: 236
Interventions	**Targeted domains** Group 1: aerobic exercise + diet Group 2: resistance training + diet **Intervention description** Group 1: individualised program that consisted of aerobic exercise at intensity corresponding to 55% to 65% of VO2max gradually increased in first 6 months + personal dietary counselling (based on questionnaire) Group 2: individualised strength-training program, based on measurement of one repetition maximum gradually increased in first 6 months personal+ dietary counselling (based on questionnaire) **Intervention timing** Group 1: 5 x 60 minutes/week aerobic exercise. 5 individual exercise or nutrition session in 1st year and every 6 months thereafter Group 2: 2 resistance training sessions/week. 5 individual exercise or nutrition session in 1st year and every 6 months thereafter

DR's EXTRA 2010 *(Continued)*

	Intervention delivered by Exercise physiologist and nutritionist **Intervention duration** 2 years **Control group description** Oral information about general public health advice on diet and physical activity
Outcomes	**Outcomes relevant to this review** • Mini-Mental State Examination
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The subjects were asked to choose one of the identical sealed opaque envelopes that were in a mixed order and contained the group assignment."
Allocation concealment (selection bias)	Low risk	Adequate concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded to allocation due to the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Experienced research personnel who carried out CERAD tests were blinded both to the group assignment as well as baseline cognitive tests
Incomplete outcome data (attrition bias) All outcomes	Low risk	96% complete for MMSE.
Selective reporting (reporting bias)	High risk	Analysis plan not published before start trial. CERAD was obtained for all participants, but not reported as total score. Also individual tests were not reported, only selective domains.
Other bias	Low risk	No other sources of bias identified. Study was not prospectively registered.

FINGER 2015

Study characteristics

Methods	**Study design** RCT **Total study duration** 2009-2014 **Duration of follow-up** 24 months
Participants	**Population description**

FINGER 2015 *(Continued)*

Cognitive performance at the mean level or slightly lower that expected for age
Risk population description (if applicable)
CAIDE of 6 points or higher and cognitive performance at the mean level or slightly lower that expected for age

Baseline age
Mean 69.3 years

Setting of study
Healthcare practices

Inclusion criteria
Age 60-77, CAIDE > 6, 1 insufficient CERAD section

Exclusion criteria
Previously diagnosed dementia, suspected dementia, MMSE < 20, disorders affecting safe engagement, severe loss of vision, hearing or communicative ability, disorders preventing co-operation, coincident participation in other intervention trial

Participants randomised
Total: 1260
Intervention: 631
Control: 629

Interventions

Targeted domains
Diet, physical exercise, cognitive training, social activities, management of metabolic and vascular risk factors

Intervention description
Diet: nutritionists, 3 individual sessions, 7-9 group sessions/physical exercise training programme by physiotherapists at the gym, muscle strength (1-3 x per week), aerobic exercise (2- 5x per week),/ cognitive training: 10 group sessions by psychologists and individual computerised training form home or study site (72 sessions of 10-15 minutes)/social activities through group meetings/management of metabolic and vascular risk factors/3 meetings with nurse and 3 with physician for measurements and recommendations for lifestyle management.

Intervention timing
6 monthly assessments with study nurse. Nutrition: 3 individual and 7-9 group sessions. Physical exercise: 1-3/week muscle strength, 2-5/week aerobic. Cognitive training: 10 group, 72 individual sessions.

Intervention delivered by
Nutritionists, physiotherapists, psychologists, and physicians

Intervention duration
24 months

Control group description
Regular health advice

Outcomes

Outcomes relevant to this review

- Composite cognition score, defined by the use of a neuropsychological test battery
- Mini-Mental State Examination
- Mortality
- Myocardial infarct events
- Stroke events
- Quality of life, defined by RAND-36 (SF-36) score
- Activities of daily living, assessed by using multiple ADL related questionnaires

Notes

FINGER 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site after baseline by the study nurse."
Allocation concealment (selection bias)	Low risk	Adequate concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel could not be blinded due to the nature of the intervention. Participants were blinded as much as possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to study allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	95% complete outcome data, no indicators of selective drop out
Selective reporting (reporting bias)	Low risk	MMSE was reported as secondary outcome in protocol paper, though not published afterwards. The findings on the MMSE were made available to us by the study authors upon request.
Other bias	Low risk	No other sources of bias identified

HATICE 2019

Study characteristics

Methods	**Study design** RCT **Total study duration** 2015-2018 **Duration of follow-up** 18 months
Participants	**Population description** Community-dwelling *Risk population description (if applicable)* Two or more cardiovascular risk factors (i.e., hypertension, dyslipidaemia, overweight, current smoking, or physical inactivity), or a history of cardiovascular disease (i.e. stroke, transient ischaemic attack, myocardial infarction, angina pectoris, or peripheral arterial disease) or diabetes, or both. **Baseline age** Median: 69 years **Setting of study** Assessment at study centres, intervention digital **Inclusion criteria**

HATICE 2019 *(Continued)*

	> 64 year, two or more cardiovascular risk factors (i.e. hypertension, dyslipidaemia, overweight, current smoking, or physical inactivity), or a history of cardiovascular disease (i.e. stroke, transient ischaemic attack, myocardial infarction, angina pectoris, or peripheral arterial disease) or diabetes, or both, and access to the Internet using a laptop, computer or tablet. **Exclusion criteria** Dementia, computer illiteracy, any condition to hinder 18-month follow-up, MMSE < 24 **Participants randomised** *Total*: 2724 *Intervention*: 1389 *Control*: 1335
Interventions	**Targeted domains** Smoking, blood pressure, cholesterol, diabetes, weight, physical activity, and nutrition **Intervention description** Intervention group participants received access to a secure Internet-based platform with remote support from a coach trained in motivational interviewing and lifestyle behaviour advice, based on the stages of change model. The platform was designed to facilitate self-management of cardiovascular risk factors by defining health priorities, goal setting, monitoring progress with (graphical) feed back, and a combination of automated and personal feedback from the coach, Coaches motivated participants via a computer messaging system to set at least one goal to improve a cardiovascular risk factor, encouraged them to interact with the platform, set additional goals over time, and provided motivating feedback. **Intervention timing** Continuous coaching, goal setting at start, boost-call at 12 months **Intervention delivered by** HATICE health coaches **Intervention duration** 18 months **Control group description** Participants allocated to the control condition had access to a static platform, similar in appearance, with limited general health information only, without interactive components or a remote coach.
Outcomes	**Outcomes relevant to this review** • Composite cognitions score, defined by a combination of MMSE, Stroop 1–3, Rey Recall, Rey Recognition and Verbal fluency • Mini-Mental State Examination • Mortality incidence • Cardiovascular events • Myocardial infarct events • Stroke events • Activities of daily living, defined by the late life function and disability instrument
Notes	some of the authors of this Cochrane Review were involved in this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After completion of the baseline assessment, participants were individually randomly assigned in a 1:1 ratio using a central, computer-generated sequence, which was linked to the online case record form."

HATICE 2019 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "After completion of the baseline assessment, participants were individually randomly assigned in a 1:1 ratio using a central, computer-generated sequence, which was linked to the online case record form."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Complete masking of participants and the coaches delivering the intervention was not possible because of the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent assessor unaware of treatment allocation did the final assessment, including outcome assessment."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Complete outcome data for MMSE 91% of participants in control, 86% in intervention. For composite cognition score 86,6% complete in control group 81.1% in intervention group This is differential"
Selective reporting (reporting bias)	Low risk	Reported outcomes congruent with protocol and trial registration.
Other bias	Low risk	No other sources of bias identified

Lee 2014

Study characteristics	
Methods	**Study design** RCT **Total study duration** 2008-2010 **Duration of follow-up** 18 months
Participants	**Population description** Community-dwelling *Risk population description (if applicable)* Not applicable **Baseline age** Mean 77.1 years **Setting of study** Geriatric mental health community centres **Inclusion criteria** Regular attendee at senior citizen centres and at least 60 years **Exclusion criteria** History of significant hearing or visual impairment that rendered interview participation difficult, a history of neurological disorders (e.g. dementia, stroke, Parkinson's disease, brain tumour, head injuries, and active epilepsy), a psychiatric illness (e.g. schizophrenia, mental retardation, severe depression, and mania), the use of psychotropic medications, or a history of substance abuse. **Participants randomised** *Total*: 1115 *Intervention*: Group 1: 215, group 2: 241, group 3: 211, group 4: 236

Lee 2014 *(Continued)*

	Control: 212
Interventions	**Targeted domains** Group 1: physical activity, cognitive and social activities, alcohol, smoking, lean body mass and healthy diet Group 2: physical activity, cognitive and social activities, alcohol, smoking, lean body mass and healthy diet Group 3: physical activity, cognitive and social activities, alcohol, smoking, lean body mass and healthy diet Group 4: physical activity, cognitive and social activities, alcohol, smoking, lean body mass and healthy diet **Intervention description** Group 1: telephonic care management (10-15 minutes) reviewing participants' lifestyle behaviour Group 2: telephonic care management and educational items Group 3: health worker-initiated visit care management (15-20 minutes) reviewing participants' lifestyle behaviour Group 4: health worker-initiated visit care management (15-20 minutes) reviewing participants' lifestyle behaviour plus behavioural reinforcement through rewards such as golden medals **Intervention delivered by** Nursed specialised in lifestyle management **Intervention timing** Group 1: Every two months Group 2: Monthly Group 3: Every two months Group 4: Every two months **Intervention duration** 18 month **Control group description** Lifestyle advice
Outcomes	**Outcomes relevant to this review** • Mini-Mental State Examination
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 35 senior citizen center clusters were randomly assigned to five groups (group descriptions to follow) using random allocation sequences in Stata version 11.0 (StataCorp, College Station, Tex., USA)."
Allocation concealment (selection bias)	Low risk	Adequate concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Due to the nature of the interventions, we were unable to blind the health workers and study participants."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Practice nurses who were blinded to group allocation performed the MMSE at baseline and the following 18 months of the intervention."

Lee 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Flowchart unclear: Not clear whether people died before or after randomisation. It seems like people were first randomised and afterwards they were asked if they were willing to participate More than half of the participants dropped out during the intervention and were not retrieved for final assessment.
Selective reporting (reporting bias)	Unclear risk	No protocol found. No trial registration.
Other bias	High risk	Poor statistics analyses: the unit of analysis was the cluster, whereas the unit of analysis should be the individual and then taking into account a cluster effect by e.g. random-effects models. The outcome (MMSE) was imputed only single (not by multiple imputation), thereby not taking random variation into account for the confidence interval. Only (adjusted) means for each group is shown. It is unclear for the control group what the follow-up MMSE is, therefore the reported effect sizes cannot be fully interpreted.

Li 2018

Study characteristics	
Methods	**Study design** RCT **Total study duration** 2013-2017 **Duration of follow-up** 2 years
Participants	**Population description** Mine workers *Risk population description (if applicable)* Hypertension (SPB > 140, DBP > 90 or taking antihypertensive drugs 2 weeks before the study) **Baseline age** Mean 45.6 years **Setting of study** Assessment during health checks **Inclusion criteria** Hypertension, mining staff, participating in annual health check **Exclusion criteria** Incomplete data, refusal of intervention and follow-up, secondary hypertension, diabetes **Participants randomised** *Total*: 510 *Intervention*: group 1: 116, group 2: 209 *Control*: group 1:38, group 2:147
Interventions	**Targeted domains** Group 1: (Participants using medication group) Lifestyle, nutrition, hypertension, physical activity, smoking cessation, weight loss, alcohol, mental stress Group 2: (Participants not using medication group) Lifestyle, nutrition, hypertension, physical activity, smoking cessation, weight loss, alcohol, mental stress

Li 2018 *(Continued)*

	Intervention description Group 1: health education and counselling, seminars, organisation of sport events, recommendation of DASH diet Group 2: health education and counselling, seminars, organisation of sport events, recommendation of DASH diet **Intervention timing** Group 1:Health education and behaviour counselling monthly. Regular health seminars and free education material on prevention of hypertension every 3 months. Monthly SMS reminders to improve lifestyle. Monthly phone calls concerning blood pressure and lifestyle Group 2: Health education and behaviour counselling monthly. Regular health seminars and free education material on prevention of hypertension every 3 months. Monthly SMS reminders to improve lifestyle. Monthly phone calls concerning blood pressure and lifestyle **Intervention delivered by** Physicians **Intervention duration** 2 years **Control group description** Group 1 (compared to intervention group 1): medication + no lifestyle intervention Group 2 (compared to intervention group 2): no medication + no lifestyle intervention
Outcomes	**Outcomes relevant to this review** • Montreal Cognitive Assessment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomised by working district; workers in Jinduichen area to intervention group, workers in Hancheng area to control group. Only 2 districts.
Allocation concealment (selection bias)	High risk	All participants randomised in 2 groups based on their location, group allocation could be foreseen.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Personnel was blinded to group allocation, however, not clear how this was operationalised as blinding of the intervention is nearly impossible due to the nature of the study. Participants were blinded to group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study reports blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors report no dropout from the study (at all). No attrition or excluded participants
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	High risk	No individual randomisation, no clear description of source population, unclear statistics (oneway-ANOVA for 2 group comparison)

Look AHEAD 2017

Study characteristics	
Methods	**Study design** RCT **Total study duration** 2001-2014 **Duration of follow-up** 10-13 years
Participants	**Population description** Community-dwelling *Risk population description (if applicable)* Diabetes mellitus type 2 + overweight/obese **Baseline age** Mean 58.8 years **Setting of study** Study centres **Inclusion criteria** 45–76 years old, BMI ≥ 25 kg/m2 (≥ 27 kg/m^2 if currently taking insulin), Type 2 diabetes mellitus **Exclusion criteria** Glycated haemoglobin (HbA1c) > 11%, systolic/diastolic blood pressure ≥ 160/100 mmHg, and triglycerides ≥ 600 mg/dL, factors that may limit adherence to interventions or affect conduct of the trial **Participants randomised** *Total*: 5145 *Intervention*: 2570 *Control*: 2575
Interventions	**Targeted domains** Weight loss, physical activity **Intervention description** Goal of weight loss of 7%, targeted daily calorie goals of 1,200– 1,800 according to initial weight and ≥ 175 minutes/week of physical activities such as brisk walking. **Intervention timing** Intervention sessions occurred weekly at months 1–6 and then tapered to 3 per month for the remainder of the first year, 6 months, and monthly thereafter, with additional support with monthly phone or e-mail contacts. **Intervention delivered by** Look AHEAD study staff **Intervention duration** Mean 9.8 years (range 8.4-11.1) **Control group description** Three group educational/social support sessions each year for 4 years after randomizations of the last volunteer
Outcomes	**Outcomes relevant to this review** • Incidence of dementia, as assessed by an independent outcome committee • Incidence of mild cognitive impairment, as assessed by an independent outcome committee

Look AHEAD 2017 *(Continued)*

- Mortality
- Cardiovascular events
- Myocardial infarct events
- Stroke events

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From protocol paper: "Eligible participants are randomly assigned to either diabetes support and education or lifestyle intervention using a web-based data management system that verifies eligibility. Randomization is stratified by clinical center and blocked with random block sizes."
Allocation concealment (selection bias)	Low risk	From protocol "Eligible participants are randomly assigned to either diabetes support and education or lifestyle intervention using a web-based data management system that verifies eligibility."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported if participants or personnel were blinded during intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	From article: "Data were collected by trained and masked staff"
Incomplete outcome data (attrition bias) All outcomes	High risk	Around 74% of participants had data on the primary outcome.
Selective reporting (reporting bias)	Low risk	The cognitive outcomes were later added to the design. However, there are no indications that any of the collected outcomes for this purpose were not or selectively reported.
Other bias	Unclear risk	Commercial funding sources reported. Exact role not clear.

MAPT 2017

Study characteristics

Methods	**Study design** RCT **Total study duration** 2008-2014 **Duration of follow-up** 36 months
Participants	**Population description** Community-dwelling *Risk population description (if applicable)*

MAPT 2017 *(Continued)*

At least one of the following: spontaneous memory complaint expressed to their physician, limitation in one instrumental activity of daily living, or slow gait speed (≤ 0.8 meter/second, or more than 5 seconds to walk 4 metre).

Baseline age
Mean 75.3 years

Setting of study
Study (memory) centre

Inclusion criteria
Age ≥ 70, community-dwelling and at least one of the following: spontaneous memory complaint expressed to their physician, limitation in one instrumental activity of daily living, or slow gait speed (≤ 0.8 metre/second, or more than 5 seconds to walk 4 metre)

Exclusion criteria
MMSE < 24,dementia, difficulties in basic activities of daily living, taking polyunsaturated fatty acids (PUFA) at baseline

Participants randomised
Total: 1680
Intervention: Group 1: 417, group 2: 420
Control: 420

Interventions

Targeted domains
Cognitive stimulation, physical activity, and nutrition, management of cardiovascular risk factors and functional impairments

Intervention description
Group 1: Cognitive training and psychical activity small group sessions. Nutritional advice and preventive consultation to optimise risk factors. Supplementation of PUFA.
Group 2: Cognitive training and psychical activity small group sessions. Nutritional advice and preventive consultation to optimise risk factors. Supplementation with placebo.

Intervention timing
Group 1: Two capsules of PUFA daily and 2-hour group sessions focusing on three domains (cognitive stimulation, physical activity, and nutrition) and a preventive consultation (at baseline, 12 months, and 24 months) with a physician to optimise management of cardiovascular risk factors and detect functional impairments. Twelve small group sessions of the multi-domain intervention were done in the first 2 months of the trial. Each session included 60 minutes of cognitive training, 45 minutes of advice about and demonstrations of physical activity and 15 minutes of nutritional advice.
Group 2: Two capsules of placebo daily and 2-hour group sessions focusing on three domains (cognitive stimulation, physical activity, and nutrition) and a preventive consultation (at baseline, 12 months, and 24 months) with a physician to optimise management of cardiovascular risk factors and detect functional impairments. Twelve small group sessions of the multi-domain intervention were done in the first 2 months of the trial. Each session included 60 minutes of cognitive training, 45 minutes of advice about and demonstrations of physical activity and 15 minutes of nutritional advice.

Intervention delivered by
Preventive consultation by physician, providers of other interventions not explicitly reported

Intervention duration
36 months

Control group description
Daily placebo pills

Outcomes

Outcomes relevant to this review

- Composite cognition score, defined by Free and total recall of the Free and Cued Selective Reminding test, ten Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test
- Mini Mental State Examination

MAPT 2017 *(Continued)*

- Cardiovascular events
- Activities of daily living, defined by Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument (ADCSADLPI)
- Participants adherent to the intervention, defined by counting the number of capsules returned by participants (for supplementation) and/or the percentage of intervention sessions attended (for the multi-domain intervention). Participants were adherent if attended > 75% and 75% PUFA

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomisation procedure (done by ClinInfo, a subcontractor) was used with block sizes of eight and stratification by centre."
Allocation concealment (selection bias)	Low risk	Quote: "A clinical research assistant, who was not involved in the assessment of participants, used a centralised interactive voice response system to identify which group to allocate the participant to, and which lot number to administer."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "In view of the nature of the multi-domain intervention, the study was unblinded for this component, but the independent neuropsychologists who were trained to assess cognitive outcomes were blinded to group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The independent neuropsychologists who were trained to assess cognitive outcomes were blinded to group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	90% complete outcome data, number of excluded did not differ significantly between groups. Excluded participants were older and with lower education.
Selective reporting (reporting bias)	Low risk	Congruent with protocol and registration. Primary outcome changed during the study. However, outcome was changed before data were deblinded.
Other bias	Low risk	No other bias detected

preDIVA 2016

Study characteristics

Methods

Study design
RCT

Total study duration
2006-2015

Duration of follow-up
6-8 years

Participants

Population description
Community-dwelling
Risk population description (if applicable)
Not applicable

preDIVA 2016 *(Continued)*

	Baseline age Mean 74.5 years **Setting of study** General practitioner (GP) practices **Inclusion criteria** 70-78 years, registered with GP **Exclusion criteria** Dementia, other diseases likely to hinder long term follow-up **Participants randomised** *Total*: 3526 *Intervention*: 1890 *Control*: 1636
Interventions	**Targeted domains** Smoking, diet, physical activity, weight, blood pressure, diabetes, dyslipidaemia. **Intervention description** Assessment of risk profile and individually tailored lifestyle advice based on guidelines and supported by motivational interviewing by the practice nurse **Intervention delivered by** Practice nurses **Intervention timing** Four-monthly with practice nurse, for 6 years. Two-yearly blood glucose and lipids **Intervention duration** 6 years **Control group description** Usual care
Outcomes	**Outcomes relevant to this review** • Incident dementia, as assessed by an independent outcome committee, diagnosis re-evaluated after 1 year • Mini-Mental State Examination • Mortality • Cardiovascular events • Myocardial infarction events • Stroke events • Activities of daily living, defined by the Amsterdam Linear Disability Scale • Participants adherent to intervention, defined as exclusion of intervention group participants who on average had received < 2 intervention visits per year upon reaching a study endpoint (dementia/death/end of trial), and control group participants who had received > 2 undue intervention visits per year.
Notes	some of the authors of this Cochrane Review were involved in this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "..centralised computer algorithm was used by the Clinical Research Unit, not involved in the study in any other way."

preDIVA 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "after completion of all baseline visits at a health-care centre (to avoid non-random differences in consent rates between general practices in the same building), cluster randomisation took place with general practice as the unit of randomisation, to minimise contamination at the level of general practice."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind personnel due to the nature of the study. Participants were blinded to group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All outcome assessors were masked to group allocation and were not involved in intervention activities. The final clinical assessment was done by an independent investigator who was masked to group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Follow-up data for the primary outcome of dementia were obtained for 3454 (98·0%) participants, yielding 21 341 person-years. Information about survival was available for 3519 (99·8%) participants."
Selective reporting (reporting bias)	Low risk	Outcomes are the same as reported in protocol and trial register
Other bias	Low risk	No other sources of bias identified

Taiwan Health 2020

Study characteristics	
Methods	**Study design** RCT **Total study duration** 2014-2017 **Duration of follow-up** 12 months
Participants	**Population description** Community-dwelling prefrail/frail people *Risk population description (if applicable)* Subjective memory impairment and/or loss of ≥ 1 instrumental activities of daily living (IADL), and/or timed 6-mertre walk speed ≤ 1 metre/second **Baseline age** Mean 75.1 years **Setting of study** Community centres **Inclusion criteria** ≥ 65 year, currently receiving Taiwan National Health Insurance services; subjective memory impairment and/or loss of ≥ 1 instrumental activities of daily living (IADL), and/or timed 6-metre walk speed ≤ 1 metre/second; and competence to sign informed consent personally and to comply with study procedures **Exclusion criteria** Age < 65 year, dementia diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition or suspected by a clinician; self/caregiver-reported total or partial dependence for

Taiwan Health 2020 *(Continued)*

	ADL, or major illness with life expectancy < 6 months; interviewer-adjudicated severe hearing or visual impairment; documented major depression or anxiety, or other major illness that may jeopardize compliance (at investigators' discretion); institutionalisation; or current participation in other clinical studies or research **Participants randomised** *Total*: 1082 *Intervention*: 549 *Control*: 533
Interventions	**Targeted domains** Physical exercise, cognitive training, nutrition advice, disease education **Intervention description** The routine curriculum comprised 45 minutes of physical fitness activities, specifically aerobic exercises, resistance work, and balance and flexibility training; 1 hour of cognitive training, including reasoning and memory exercises; and 15 minutes of general nutrition advice, including a balanced diet and adequate protein Participants were actively encouraged to practice on their own at home. In addition, every 3 or 4 months, some activities were curtailed, and a visiting doctor instead gave a 30 to 60 minutes class on preventing/managing chronic disease, which included education about healthy aging, dementia, cardiovascular risk factors, osteoporosis, and sarcopenia **Intervention timing** The Efficacy Study programme scheduled four structured 2-hour training sessions in the first month, two during the second, and one in each of the next 10 months. In addition, every 3 or 4 months, some activities were curtailed, and a visiting doctor instead gave a 30 to 60 minutes class on preventing/managing chronic disease. **Intervention delivered by** Healt care professionals (e.g. fitness coach, physical therapist, occupational therapist, and dietician) or trained staff **Intervention duration** 12 months **Control group description** Conventional health education in the Efficacy Study control group entailed periodic telephone calls (~3 monthly) by local research site staff to offer participants health education and advice (the intervention group did not receive such calls)
Outcomes	**Outcomes relevant to this review** • Montreal Cognitive Assessment • Acticities of daily living, defined by the Instrumental Activities of Daily living
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Independent researchers not involved in assessing outcomes used a random number sequence generated by Excel 2013 (Microsoft, Redmond, WA, USA) to allocate participants in clusters, by simple direct sampling, 1:1 to intervention or control groups."
Allocation concealment (selection bias)	Low risk	Quote: "Independent researchers not involved in assessing outcomes used a random number sequence generated by Excel 2013 (Microsoft, Redmond, WA, USA) to allocate participants in clusters, by simple direct sampling, 1:1 to intervention or control groups. Opaque sealed envelopes were used to conceal the interventions allocated from participants and assessors."

Taiwan Health 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel was not blinded for treatment allocation due to the nature of the study. Participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ".. to conceal the intervention allocated from participants and assessors. "
Incomplete outcome data (attrition bias) All outcomes	High risk	High loss during follow-up. 74,7% in intervention and 70.4% in control group available for analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol published. Trial registration only states primary outcome, secondary outcomes not reported
Other bias	Low risk	No other bias identified

ADL: activities of daily living; **CAIDE:** Cardiovascular Risk Factors, Aging, and Incidence of Dementia; **CERAD:** Consortium to Establish a Registry for Alzheimer's Disease; **DASH Diet:** Dietary Approaches to Stop Hypertension; **DBP:** diastolic blood pressure; **MMSE:** Mini-Mental State Examination; **RCT:** randomised controlled trial; **SBP:** systolic blood pressure; SF: Short Form 36.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Araki 2012	Wrong outcomes
Assaf 2016	Wrong intervention
Bickel 2012	Wrong outcomes
Birmingham 2020	Wrong intervention
Blacker 2006	Wrong intervention
Chhetri 2018	Not the original paper
Drks 2016	Wrong outcomes
Drks 2017	Study not finished yet
Espeland 2018	Not the original paper
Frenn 2003	Wrong outcomes
Ganz 2007	Wrong outcomes
Guerville 2019	Wrong outcomes
Hatch 2014	Wrong intervention
Hayden 2018	Study not finished yet
Kivipelto 2014	Not the original paper

Study	Reason for exclusion
Lam 2015	Wrong study design
Lehtisalo 2016	Wrong study design
Liu 2018	Wrong comparator
Manfredi 2013	Wrong study design
Mayer-Berger 2014	Wrong outcomes
Murchie 2003	Wrong outcomes
Oswald 2002	Wrong patient population
Petersen 2005	Wrong intervention
Resnick 2009	Wrong outcomes
Solomon 2018	Not the original paper
Voss 2019	Wrong patient population
Zijlstra 2009	Wrong intervention

Characteristics of ongoing studies *[ordered by study ID]*

Agewell.de

Study name	Agewell.de
Methods	Multi-centric cluster-randomised controlled trial
Participants	Community-dwelling GP patients who are 60–77 years old with an increased CAIDE Dementia Risk Score
Interventions	During the 2-year follow-up period, participants of intervention group A (advanced) will receive a systematic comprehensive multi-component intervention program, including: • advice on healthy nutrition, based on the guidelines of the German Nutrition Society (DGE); • exercises for strength, balance and flexibility on two days per week; aerobic training (3–5 days per week for 20–30 minutes) planned individually with the participant; • cognitive training with tablet computers, using the cognitive training software “NeuroNation”, three times per week; • enhancement of social engagement, planned individually with the participant; • if necessary, feedback on vascular risk factors (e.g. smoking, medical history) and ways to reduce the respective risk; • assessment of depressive symptoms and underlying risk factors (e.g. bereavement, grief); if necessary, patients will be encouraged to contact their GP who will provide adequate support and care (e.g. referring participants to groups, psychiatrists, psychotherapists, psychiatric hospitals); written information on addresses and helplines which can be contacted in case of grief and/or depressive symptoms; • optimisation of medication.

Agewell.de *(Continued)*

	Participants of intervention group B (basic) will receive GP treatment as usual and general health advice related to the components of intervention A.
Outcomes	Primary outcome • Cognitive performance (neuropsychological test battery) Secondary outcomes • Mortality • Nursing home placement • Instrumental activities of daily living/activities of daily living • Quality of life, depressive symptoms, social inclusion • Motivation for behavior change • Cost-effectiveness
Starting date	11/07/2018
Contact information	Universität Leipzig, Medizinische Fakultät, Institut für Sozialmedizin, Arbeitsmedizin und Public Health (ISAP) Ms. M.A. Andrea Zülke Philipp-Rosenthal-Str. 55 04103 Leipzig Germany Telephone: +49 341 9715483 E-mail: andrea.zuelke at medizin.uni-leipzig.de
Notes	Trial identifier (DRKS-ID): DRKS00013555

AU-ARROW

Study name	the AUstralian-multidomain Approach to Reduce dementia Risk by prOtecting brain health with lifestyle intervention (AU-ARROW)
Methods	Randomised controlled trial
Participants	Community-dwelling older adults (55 to 75 years old) at risk of cognitive decline and dementia
Interventions	Randomisation in to one of three groups: • usual care; • health education and support; • multi-domain intervention group.
Outcomes	Primary outcome • Change in cognition (NTB) Secondary outcomes • Blood and cerebrospinal fluid (CSF) biomarkers • Brain imaging—amyloid and fluorodeoxyglucose PET • MRI • Retinal imaging

AU-ARROW *(Continued)*

Starting date	Funded, recruitment pending
Contact information	Macquarie University, Australia Tejal Shah, PhD tejal.shah@mq.edu.au
Notes	

Bai 2017

Study name	A randomised controlled multimodal intervention trial in patients with ischaemic stroke in Shandong, China
Methods	Single-blind randomised controlled intervention study
Participants	Tertiary hospital patients with first-ever ischaemic stroke, age 40 years or older, and no loss of consciousness.
Interventions	Patients in the intervention group receive an additional personalised multilevel intervention procedure that consists of motivational interviewing for behavioural change (smoking, alcohol use, and medical adherence), dietary advice, and regular monitor of major cardiometabolic risk factors (high blood pressure, high serum cholesterol, and high blood glucose). Patients in the control group receive standard care and treatment according to current guidelines.
Outcomes	Primary outcomes • Recurrent stroke • Functional ability (at year 1) • Cognitive performance (at year 2) The secondary outcomes • Survival • Quality of life • Depression
Starting date	15/10/2015
Contact information	Shandong Jining Medical University Prof Bai Bo bbai@mail.jnmc.edu.cn http://www.jnmc.edu.cn
Notes	Trial identifier: ChiCTR-IOR-16007741 Reached out to investigators to verify if study is completed, but did not receive a response after the second reminder.

J-MINT

Study name	Japan-multimodal intervention Trial for prevention of dementia (J-MINT)
Methods	Randomised controlled trial

J-MINT *(Continued)*

Participants	Older adults with cognitive impairment (66-85 years old)
Interventions	Multi-domain intervention including the management of lifestyle-related disease, exercise, nutritional guidance, and cognitive training.
Outcomes	Primary outcome • Change in a composite score of cognitive function from baseline to a 18-month follow-up. Secondary outcomes • Changes in a composite score of cognitive tests from baseline to a 6/12-month follow-up • Changes in scores of each cognitive test from baseline to a 6/12/18-month follow-up. • Changes in ADL scores from baseline to a 6/18-month follow-up. • Incident dementia.
Starting date	25/11/2019
Contact information	Hidenori Arai National Center for Geriatrics and Gerontology Department of Geriatric Medicine 0562-46-2311 harai@ncgg.go.jp
Notes	Trial identifier: UMIN000038671

Maintain Your Brain

Study name	Maintain Your Brain (MYB)
Methods	Randomised controlled trial
Participants	Non-demented community-dwelling 55 to 77 year olds
Interventions	Intervention: personalised modular internet-based multi-domain coaching in four thematic areas Control: non-interactive web-based advice via internet
Outcomes	Primary outcome • Global cognitive functioning (NTB) Secondary outcomes • Incident dementia • Change in dementia risk (ANU-ADRI-SF total score) • Change in cognitive domain scores and individual cognitive tests
Starting date	19/06/2018
Contact information	Dementia Collaborative Research Centre Prof Henry Brodaty h.brodaty@unsw.edu.au
Notes	Trial identifier: ACTRN 12618000851268

MEDEX

Study name	Mindfulness-based stress reduction, health Education and Exercise (MEDEX)
Methods	2×2 factorial design randomised controlled trial
Participants	Community-living older adults age 65 to 84 years, with self-reported cognitive complaints that are a normal part of aging.
Interventions	Experimental: Mindfulness-Based Stress Reduction (MBSR) • MBSR consists of a brief introductory meeting, eight weekly 2.5-hour classes, and a retreat, followed by monthly booster sessions for approximately 15 months. Content includes instruction in mindfulness meditation practices, gentle mindful movement, and exercises to enhance mindfulness in everyday life. Experimental: exercise • The exercise protocol is optimal for improving aerobic fitness and insulin sensitivity in older adults, as well as improving strength and balance and reducing indices of frailty.It consists of classes twice weekly for 6 months, building up to 1.5 hours, under the direct supervision of trained exercise instructors, followed by once weekly classes for 12 months. Experimental: MBSR + exercise • This condition will receive both MBSR and exercise as described above. Participants in this condition will come in once weekly to receive MBSR and twice weekly to receive exercise classes, with at-home exercise the other two days as well as daily, at-home mindfulness practice. After the initial classes participants will also attend additional weekly or monthly sessions until completion of the study. Active Comparator: health education • Health education is a group-based intervention that increases health-related knowledge and action. Health education improves chronic disease management.Health education consists of 10 weekly 2.5-hour classes, followed by monthly classes for approximately 15 months.
Outcomes	Primary outcomes • Change in memory composite score • Change in cognitive control composite score Secondary outcomes • Self-report questionnaires assessed via Ecological Momentary Assessment (EMA) measuring everyday cognition, anxiety, depression, and participation in social roles and activities. • Instrumental Activities of Daily Living measure
Starting date	April 2015. Estimated completion date June 2021
Contact information	Eric J Lenze, MD Washington University School of Medicine
Notes	Trial identifier: NCT02665481

MIND-CHINA

Study name	Multimodal INtervention to delay Dementia and disability in rural China (MIND-CHINA)

MIND-CHINA *(Continued)*

Methods	Cluster-randomised controlled trial
Participants	Non-demented and non-disabled participants aged 60 to 79 years
Interventions	Randomisation into 1 of 3 groups • Regular health care services provided by government • Vascular intervention group that will receive intensive medical treatment to improve the control of three major vascular risk factors (high blood pressure, high blood glucose, and dyslipidaemia) • Multi-domain intervention group that will receive guidelines of healthy lifestyle and diet, physical exercise, promotion of personalized leisure activities, as well as cognitive training, in addition to intensive management of major vascular risk factors
Outcomes	Primary outcome • Global cognitive functioning with NTB Secondary outcomes • Physical function • Incident mild cognitive impairment (MCI) and dementia (after 5 years of follow-up) • Occurrence of cardiovascular events
Starting date	01/03/2018
Contact information	Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China. Yongxiang Wang wang-yongxiang@hotmail.com
Notes	Trial registration: ChiCTR1800017758

U.S. POINTER

Study name	U.S. study to protect brain health through lifestyle intervention to reduce risk (POINTER)
Methods	Randomised controlled trial
Participants	Older adults (60-79 years) who may be at increased risk for cognitive decline owing to first degree family history of significant memory impairment, sedentary lifestyle, poor diet, and suboptimum cardio-metabolic health status
Interventions	Self-guided lifestyle intervention: lifestyle modification program that is developed by the participant to meet his/her specific needs. Structured lifestyle intervention: lifestyle modification program that involves participants completing structured activities that target diet, physical exercise, and intellectual and social stimulation.
Outcomes	Primary outcome • Global cognitive functioning with NTB Secondary outcomes • Episodic memory • Executive function • Processing speed • CLinical dementia rating (CDR)

U.S. POINTER *(Continued)*	• Instrumental Activities of Daily living • Everyday cognition • Digital clock drawing test • Lifestyle composite
Starting date	8/01/2019. Estimated completion date: December 2024
Contact information	Wake Forest University Health Sciences Laura D Baker, PhD ldbaker@wakehealth.edu
Notes	Trial identifier: NCT03688126

ADL: activities of daily living; **ANU-ADRI-SF:** Australian National University Alzheimer's Disease Risk Index, Short Form; **CAIDE:** Cardiovascular Risk Factors, Aging, and Incidence of Dementia; **MRI:** magnetic resonance imaging; NTB: neuropsychological test battery**PET:**positron emission tomography

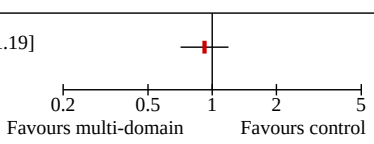
DATA AND ANALYSES

Comparison 1. Multi-domain interventions for dementia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Comparison 1. Dementia, Outcome 1. Incidence of dementia - time to event	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
1.2 Comparison 1. Dementia, Outcome 2. Incidence of dementia	2	7256	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.18]
1.3 Comparison 1. Dementia, Outcome 3. Sensitivity analysis: Incidence of dementia (exclusion of studies of low quality)	1	3454	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.73, 1.20]
1.4 Comparison 1. Dementia, Outcome 4. Sensitivity analysis: Incidence of dementia (exclusion of >20% missing values)	1	3454	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.73, 1.20]

Analysis 1.1. Comparison 1: Multi-domain interventions for dementia, Outcome 1: Comparison 1. Dementia, Outcome 1. Incidence of dementia - time to event

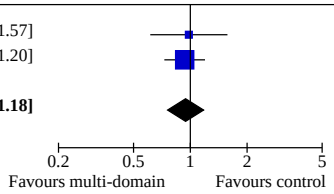
Study or Subgroup	log[Hazard Ratio]	SE	Multi-domain Total	Control Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
preDIVA 2016	-0.083	0.132	1853	1601	0.92 [0.71 , 1.19]	



Analysis 1.2. Comparison 1: Multi-domain interventions for dementia, Outcome 2: Comparison 1. Dementia, Outcome 2. Incidence of dementia

Study or Subgroup	Multi-domain Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Look AHEAD 2017	34	1918	34	1884	21.7%	0.98 [0.61 , 1.57]
preDIVA 2016	121	1853	112	1601	78.3%	0.93 [0.73 , 1.20]
Total (95% CI)		**3771**		**3485**	**100.0%**	**0.94 [0.76 , 1.18]**
Total events:	155		146			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable

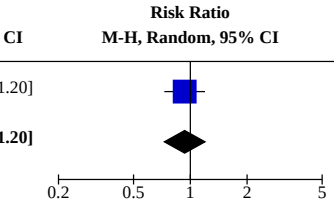


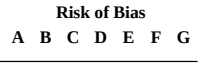
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Multi-domain interventions for dementia, Outcome 3: Comparison 1. Dementia, Outcome 3. Sensitivity analysis: Incidence of dementia (exclusion of studies of low quality)

Study or Subgroup	Multi-domain Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
preDIVA 2016	121	1853	112	1601	100.0%	0.93 [0.73 , 1.20]
Total (95% CI)		**1853**		**1601**	**100.0%**	**0.93 [0.73 , 1.20]**
Total events:	121		112			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



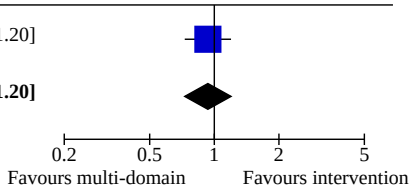


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Multi-domain interventions for dementia, Outcome 4: Comparison 1. Dementia, Outcome 4. Sensitivity analysis: Incidence of dementia (exclusion of >20% missing values)

Study or Subgroup	Multi-domain Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
preDIVA 2016	121	1853	112	1601	100.0%	0.93 [0.73 , 1.20]
Total (95% CI)		**1853**		**1601**	**100.0%**	**0.93 [0.73 , 1.20]**
Total events:	121		112			

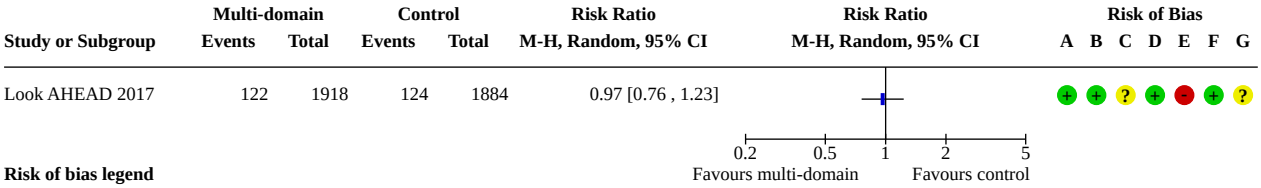
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



Comparison 2. Multi-domain interventions for mild cognitive impairment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Comparison 2. Mild Cognitive Impairment (MCI), Outome 1. Incidence of MCI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Multi-domain interventions for mild cognitive impairment, Outcome 1: Comparison 2. Mild Cognitive Impairment (MCI), Outome 1. Incidence of MCI



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

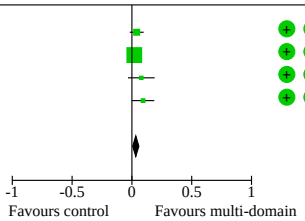
Comparison 3. Multi-domain interventions for cognitive decline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Comparison 3. Cognitive decline, Outcome 1. Composite score	3	4617	Mean Difference (IV, Random, 95% CI)	0.03 [0.01, 0.06]
3.2 Comparison 3. Cognitive decline, Outcome 2. Mini-Mental State Examination Score (MMSE)	6	8697	Mean Difference (IV, Random, 95% CI)	0.02 [-0.06, 0.09]
3.3 Comparison 3. Cognitive decline, Outcome 3. Montreal Cognitive Assessment (MoCA)	2	1554	Mean Difference (IV, Random, 95% CI)	0.76 [0.05, 1.46]
3.4 Comparison 3. Cognitive decline, Outcome 4. Sensitivity analysis: Composite score (exclusion of studies of low quality)	2	2334	Mean Difference (IV, Random, 95% CI)	0.06 [0.01, 0.10]
3.5 Comparison 3. Cognitive decline, Outcome 5. Sensitivity analysis: Mini-Mental State Examination Score (MMSE) (exclusion of studies of low quality)	3	5158	Mean Difference (IV, Random, 95% CI)	0.03 [-0.06, 0.13]
3.6 Comparison 3. Cognitive decline, Outcome 6. Sensitivity analysis: Mini-Mental State Examination Score (MMSE) (exclusion of studies with >20% missing values)	5	8238	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.08]

Analysis 3.1. Comparison 3: Multi-domain interventions for cognitive decline, Outcome 1: Comparison 3. Cognitive decline, Outcome 1. Composite score

Study or Subgroup	Multi-domain Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
FINGER 2015	0.2	0.51	591	0.16	0.51	599	19.6%	0.04 [-0.02 , 0.10]	+ + - + + + +
HATICE 2019	0	0.37	1127	-0.02	0.39	1156	67.7%	0.02 [-0.01 , 0.05]	+ + - + - + +
MAPT 2017 (1)	0.01	0.65	390	-0.069	0.64	190	5.3%	0.08 [-0.03 , 0.19]	+ + - + + + +
MAPT 2017 (2)	0.024	0.24	374	-0.069	0.64	190	7.4%	0.09 [-0.00 , 0.19]	+ + - + + + +
Total (95% CI)			**2482**			**2135**	**100.0%**	**0.03 [0.01 , 0.06]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.93, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.48 (P = 0.01)
Test for subgroup differences: Not applicable



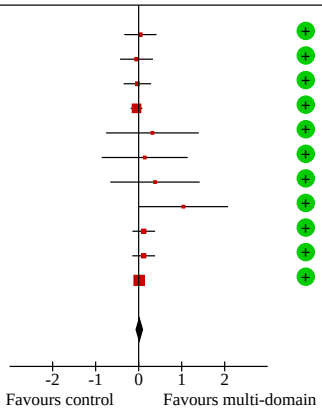
Footnotes
(1) Multidomain + placebo
(2) Multidomain + PUFA

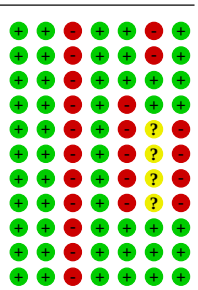
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Multi-domain interventions for cognitive decline, Outcome 2: Comparison 3. Cognitive decline, Outcome 2. Mini-Mental State Examination Score (MMSE)

Study or Subgroup	MD	SE	Multi-domain Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
DR's EXTRA 2010 (1)	0.04	0.191	224	113	3.9%	0.04 [-0.33 , 0.41]
DR's EXTRA 2010 (2)	-0.05	0.195	221	113	3.8%	-0.05 [-0.43 , 0.33]
FINGER 2015	-0.03	0.163	591	599	5.4%	-0.03 [-0.35 , 0.29]
HATICE 2019	-0.05	0.069	1194	1215	30.3%	-0.05 [-0.19 , 0.09]
Lee 2014 (3)	0.32	0.55	80	20	0.5%	0.32 [-0.76 , 1.40]
Lee 2014 (4)	0.14	0.51	111	20	0.6%	0.14 [-0.86 , 1.14]
Lee 2014 (5)	0.38	0.53	93	20	0.5%	0.38 [-0.66 , 1.42]
Lee 2014 (6)	1.04	0.53	94	21	0.5%	1.04 [0.00 , 2.08]
MAPT 2017 (7)	0.119	0.135	374	190	7.9%	0.12 [-0.15 , 0.38]
MAPT 2017 (8)	0.117	0.135	390	190	7.9%	0.12 [-0.15 , 0.38]
preDIVA 2016	0.01	0.061	1494	1330	38.7%	0.01 [-0.11 , 0.13]
Total (95% CI)			**4866**	**3831**	**100.0%**	**0.02 [-0.06 , 0.09]**

Heterogeneity: Tau² = 0.00; Chi² = 6.85, df = 10 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable





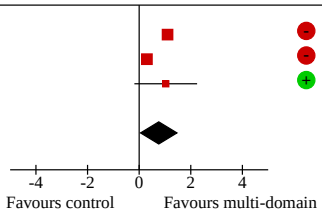
Footnotes
(1) Aerobic exercise + diet
(2) Resistance training + diet
(3) Telephonic care management bimonthly
(4) Telephonic care monthly
(5) Health worker-initiated visit care management bimonthly
(6) Health worker-initiated visit care management bimonthly + rewards
(7) Multidomain + PUFA
(8) Multidomain + placebo

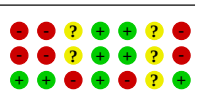
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.3. Comparison 3: Multi-domain interventions for cognitive decline, Outcome 3: Comparison 3. Cognitive decline, Outcome 3. Montreal Cognitive Assessment (MoCA)

Study or Subgroup	MD	SE	Multi-domain Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Li 2018 (1)	1.1	0.056	116	74	40.6%	1.10 [0.99 , 1.21]
Li 2018 (2)	0.3	0.022	209	73	40.9%	0.30 [0.26 , 0.34]
Taiwan Health 2020	1.03	0.62	549	533	18.5%	1.03 [-0.19 , 2.25]
Total (95% CI)			**874**	**680**	**100.0%**	**0.76 [0.05 , 1.46]**

Heterogeneity: Tau² = 0.32; Chi² = 177.80, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.11 (P = 0.03)
Test for subgroup differences: Not applicable





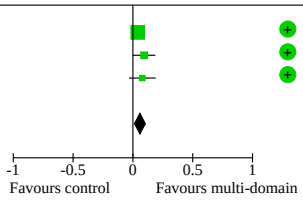
Footnotes
(1) Lifestyle intervention plus medication
(2) Lifestyle intervention without medication

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.4. Comparison 3: Multi-domain interventions for cognitive decline, Outcome 4: Comparison 3. Cognitive decline, Outcome 4. Sensitivity analysis: Composite score (exclusion of studies of low quality)

Study or Subgroup	Multi-domain Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
FINGER 2015	0.2	0.51	591	0.16	0.51	599	60.7%	0.04 [-0.02 , 0.10]
MAPT 2017 (1)	0.024	0.24	374	-0.069	0.64	190	23.0%	0.09 [-0.00 , 0.19]
MAPT 2017 (2)	0.01	0.65	390	-0.069	0.64	190	16.4%	0.08 [-0.03 , 0.19]
Total (95% CI)			**1355**			**979**	**100.0%**	**0.06 [0.01 , 0.10]**

Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable



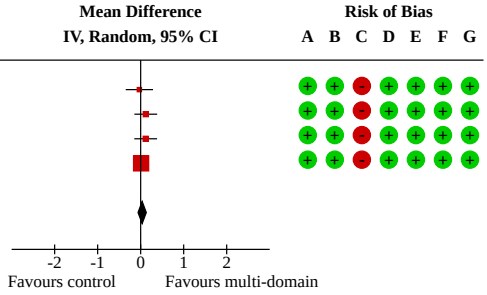
Footnotes
(1) Multidomain + PUFU
(2) Multidomain + placebo

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.5. Comparison 3: Multi-domain interventions for cognitive decline, Outcome 5: Comparison 3. Cognitive decline, Outcome 5. Sensitivity analysis: Mini-Mental State Examination Score (MMSE) (exclusion of studies of low quality)

Study or Subgroup	MD	SE	Multi-domain Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
FINGER 2015	-0.03	0.162	591	599	9.1%	-0.03 [-0.35 , 0.29]
MAPT 2017 (1)	0.119	0.135	374	190	13.2%	0.12 [-0.15 , 0.38]
MAPT 2017 (2)	0.117	0.135	390	190	13.2%	0.12 [-0.15 , 0.38]
preDIVA 2016	0.01	0.061	1494	1330	64.5%	0.01 [-0.11 , 0.13]
Total (95% CI)			**2849**	**2309**	**100.0%**	**0.03 [-0.06 , 0.13]**

Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 3 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



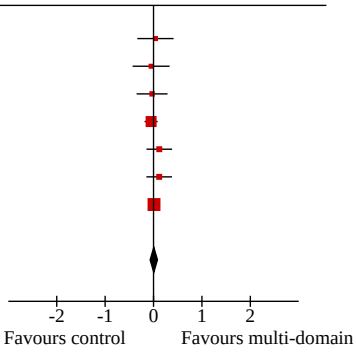
Footnotes
(1) Multidomain + PUFA
(2) Multidomain + placebo

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.6. Comparison 3: Multi-domain interventions for cognitive decline, Outcome 6: Comparison 3. Cognitive decline, Outcome 6. Sensitivity analysis: Mini-Mental State Examination Score (MMSE) (exclusion of studies with >20% missing values)

Study or Subgroup	MD	SE	Multi-domain Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
DR's EXTRA 2010 (1)	0.04	0.191	224	113	4.0%	0.04 [-0.33 , 0.41]
DR's EXTRA 2010 (2)	-0.05	0.195	221	113	3.9%	-0.05 [-0.43 , 0.33]
FINGER 2015	-0.03	0.163	591	599	5.5%	-0.03 [-0.35 , 0.29]
HATICE 2019	-0.05	0.069	1194	1215	30.9%	-0.05 [-0.19 , 0.09]
MAPT 2017 (3)	0.119	0.135	374	190	8.1%	0.12 [-0.15 , 0.38]
MAPT 2017 (4)	0.117	0.135	390	190	8.1%	0.12 [-0.15 , 0.38]
preDIVA 2016	0.01	0.061	1494	1330	39.5%	0.01 [-0.11 , 0.13]
Total (95% CI)			**4488**	**3750**	**100.0%**	**0.01 [-0.07 , 0.08]**

Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 6 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



Footnotes
(1) Aerobic exercise + diet
(2) Resistance training + diet
(3) Multidomain + PUFA
(4) Multidomain + placebo

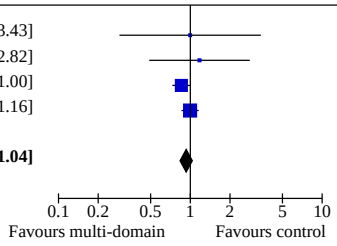
Comparison 4. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Comparison 4. Adverse events, Outcome 1. Mortality	4	11487	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.04]
4.2 Comparison 4. Adverse events, Outcome 2. Cardiovascular disease	4	11879	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.15]
4.3 Comparison 4. Adverse events, Outcome 3. Myocardial infarction	4	11965	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.75, 1.06]
4.4 Comparison 4. Adverse events, Outcome 4. Stroke	3	6822	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.38, 1.49]
4.5 Comparison 4. Adverse events, Outcome 5. Sensitivity analysis: Mortality (exclusion of studies of low quality)	2	4779	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.15]

Analysis 4.1. Comparison 4: Adverse events, Outcome 1: Comparison 4. Adverse events, Outcome 1. Mortality

Study or Subgroup	Multi-domain Events	Multi-domain Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
FINGER 2015	5	631	5	629	0.8%	1.00 [0.29 , 3.43]
HATICE 2019	11	1388	9	1333	1.5%	1.17 [0.49 , 2.82]
Look AHEAD 2017	252	2020	287	1967	46.3%	0.86 [0.73 , 1.00]
preDIVA 2016	309	1885	269	1634	51.4%	1.00 [0.86 , 1.16]
Total (95% CI)		**5924**		**5563**	**100.0%**	**0.93 [0.84 , 1.04]**
Total events:	577		570			

Heterogeneity: Tau² = 0.00; Chi² = 2.18, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable

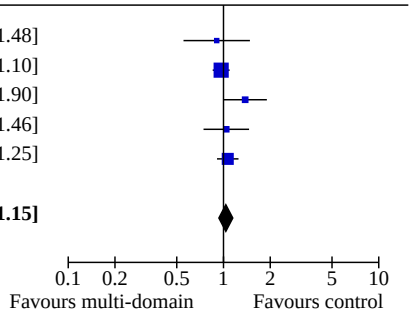


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Adverse events, Outcome 2: Comparison 4. Adverse events, Outcome 2. Cardiovascular disease

Study or Subgroup	Multi-domain Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
HATICE 2019	30	1382	32	1333	4.2%	0.90 [0.55 , 1.48]
Look AHEAD 2017	403	2570	418	2575	45.4%	0.97 [0.85 , 1.10]
MAPT 2017 (1)	109	411	40	208	9.6%	1.38 [1.00 , 1.90]
MAPT 2017 (2)	84	417	40	207	8.7%	1.04 [0.74 , 1.46]
preDIVA 2016	273	1469	228	1307	32.1%	1.07 [0.91 , 1.25]
Total (95% CI)		**6249**		**5630**	**100.0%**	**1.04 [0.93 , 1.15]**
Total events:	899		758			

Heterogeneity: Tau² = 0.00; Chi² = 4.61, df = 4 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable

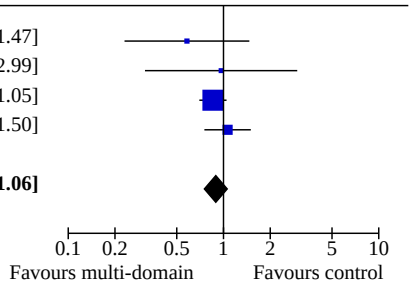


Footnotes
(1) Multidomain + PUFA
(2) Multidomain + placebo

Analysis 4.3. Comparison 4: Adverse events, Outcome 3: Comparison 4. Adverse events, Outcome 3. Myocardial infarction

Study or Subgroup	Multi-domain Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
FINGER 2015	7	631	12	629	3.3%	0.58 [0.23 , 1.47]
HATICE 2019	6	1383	6	1335	2.2%	0.97 [0.31 , 2.99]
Look AHEAD 2017	163	2570	191	2575	70.3%	0.86 [0.70 , 1.05]
preDIVA 2016	68	1503	57	1339	24.1%	1.06 [0.75 , 1.50]
Total (95% CI)		**6087**		**5878**	**100.0%**	**0.89 [0.75 , 1.06]**
Total events:	244		266			

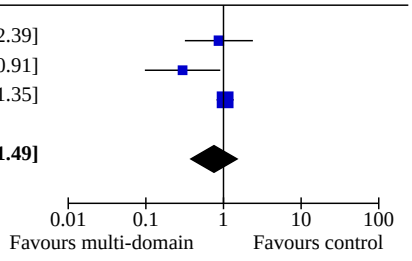
Heterogeneity: Tau² = 0.00; Chi² = 2.00, df = 3 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Adverse events, Outcome 4: Comparison 4. Adverse events, Outcome 4. Stroke

Study or Subgroup	Multi-domain Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
FINGER 2015	7	631	8	629	25.3%	0.87 [0.32 , 2.39]
HATICE 2019	4	1383	13	1335	22.5%	0.30 [0.10 , 0.91]
preDIVA 2016	120	1503	102	1341	52.2%	1.05 [0.81 , 1.35]
Total (95% CI)		**3517**		**3305**	**100.0%**	**0.75 [0.38 , 1.49]**
Total events:	131		123			

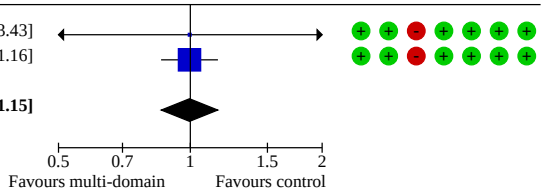
Heterogeneity: Tau² = 0.22; Chi² = 4.74, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Adverse events, Outcome 5: Comparison 4. Adverse events, Outcome 5. Sensitivity analysis: Mortality (exclusion of studies of low quality)

Study or Subgroup	Multi-domain Events	Multi-domain Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
FINGER 2015	5	631	5	629	1.4%	1.00 [0.29 , 3.43]
preDIVA 2016	309	1885	269	1634	98.6%	1.00 [0.86 , 1.16]
Total (95% CI)		**2516**		**2263**	**100.0%**	**1.00 [0.86 , 1.15]**
Total events:	314		274			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.96)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

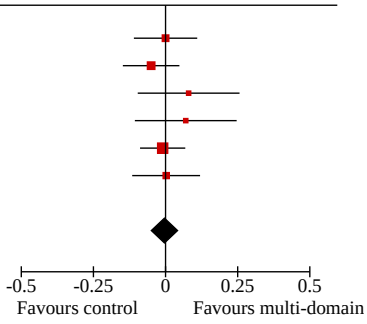
Comparison 5. Activities of daily living (ADL)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Comparison 5. Activities of daily living (ADL), Outcome 1. Effect on ADL score	5	7795	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.05, 0.04]

Analysis 5.1. Comparison 5: Activities of daily living (ADL), Outcome 1: Comparison 5. Activities of daily living (ADL), Outcome 1. Effect on ADL score

Study or Subgroup	SMD	SE	Multi-domain Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
FINGER 2015	0	0.056	603	607	17.1%	0.00 [-0.11 , 0.11]
HATICE 2019	-0.05	0.05	800	809	21.4%	-0.05 [-0.15 , 0.05]
MAPT 2017 (1)	0.08	0.09	374	160	6.6%	0.08 [-0.10 , 0.26]
MAPT 2017 (2)	0.07	0.09	390	160	6.6%	0.07 [-0.11 , 0.25]
preDIVA 2016	-0.01	0.04	1484	1326	33.4%	-0.01 [-0.09 , 0.07]
Taiwan Health 2020	0.002	0.06	549	533	14.9%	0.00 [-0.12 , 0.12]
Total (95% CI)			**4200**	**3595**	**100.0%**	**-0.00 [-0.05 , 0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 2.43, df = 5 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable



Footnotes
(1) Multidomain + PUFA
(2) Multidomain + placebo

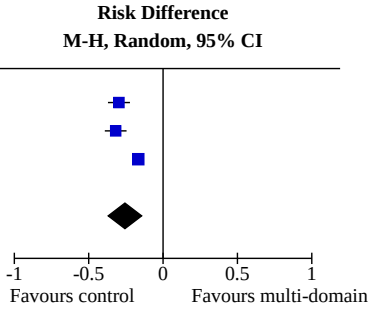
Comparison 6. Intervention adherence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Comparison 6. Intervention adherence, Outcome 1. Incidence of adherent participants	2	4557	Risk Difference (M-H, Random, 95% CI)	-0.26 [-0.37, -0.14]

Analysis 6.1. Comparison 6: Intervention adherence, Outcome 1: Comparison 6. Intervention adherence, Outcome 1. Incidence of adherent participants

Study or Subgroup	Multi-domain Events	Multi-domain Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
MAPT 2017 (1)	201	366	148	175	31.8%	-0.30 [-0.37 , -0.22]
MAPT 2017 (2)	204	387	148	175	31.9%	-0.32 [-0.39 , -0.25]
preDIVA 2016	1403	1853	1479	1601	36.3%	-0.17 [-0.19 , -0.14]
Total (95% CI)		**2606**		**1951**	**100.0%**	**-0.26 [-0.37 , -0.14]**
Total events:	1808		1775			

Heterogeneity: Tau² = 0.01; Chi² = 24.07, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4.48 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Multidomain + PUFA
(2) Multidomain + placebo

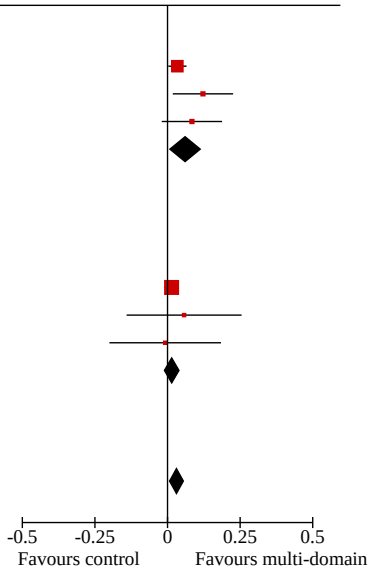
Comparison 7. Subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Subgroup analysis 1. Cognitive impairment vs no cognitive impairment. Outcome. Cognitive decline	2	2331	Mean Difference (IV, Random, 95% CI)	0.03 [0.01, 0.05]
7.1.1 Low MMSE	2	1414	Mean Difference (IV, Random, 95% CI)	0.06 [0.01, 0.11]
7.1.2 High MMSE	2	917	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.04]
7.2 Subgroup analysis 2. Participants at increased risk, defined by ApoE4 genotype. Outcome. Cognitive decline	2	2043	Mean Difference (IV, Random, 95% CI)	0.07 [0.02, 0.12]
7.2.1 Carrier	2	585	Mean Difference (IV, Random, 95% CI)	0.14 [0.04, 0.25]
7.2.2 Noncarrier	2	1458	Mean Difference (IV, Random, 95% CI)	0.04 [-0.02, 0.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 Subgroup analysis 3. Participants at increased risk, defined by CAIDE score on baseline > 6. Outcome. Cognitive decline	2		Mean Difference (IV, Random, 95% CI)	0.07 [-0.00, 0.15]

Analysis 7.1. Comparison 7: Subgroup analyses, Outcome 1: Subgroup analysis 1. Cognitive impairment vs no cognitive impairment. Outcome. Cognitive decline

Study or Subgroup	MD	SE	Multi-domain Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
7.1.1 Low MMSE						
FINGER 2015 (1)	0.034	0.016	260	244	38.0%	0.03 [0.00 , 0.07]
MAPT 2017 (2)	0.122	0.053	292	150	5.0%	0.12 [0.02 , 0.23]
MAPT 2017 (3)	0.084	0.053	318	150	5.0%	0.08 [-0.02 , 0.19]
Subtotal (95% CI)			**870**	**544**	**48.0%**	**0.06 [0.01 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 2.27 (P = 0.02)						
7.1.2 High MMSE						
FINGER 2015 (4)	0.014	0.013	329	354	49.1%	0.01 [-0.01 , 0.04]
MAPT 2017 (5)	0.057	0.101	72	40	1.4%	0.06 [-0.14 , 0.25]
MAPT 2017 (6)	-0.008	0.098	82	40	1.5%	-0.01 [-0.20 , 0.18]
Subtotal (95% CI)			**483**	**434**	**52.0%**	**0.01 [-0.01 , 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)			**1353**	**978**	**100.0%**	**0.03 [0.01 , 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 5.78, df = 5 (P = 0.33); I² = 13%						
Test for overall effect: Z = 2.54 (P = 0.01)						
Test for subgroup differences: Chi² = 2.44, df = 1 (P = 0.12), I² = 59.0%						

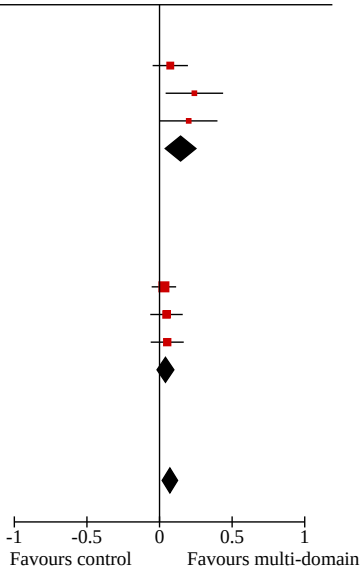


Footnotes

(1) low MMSE operationalized as MMSE score <27
(2) Multidomain + PUFA, low MMSE operationalized as MMSE score <30
(3) Multidomain + placebo, low MMSE operationalized as MMSE score <30
(4) high MMSE operationalized as MMSE score > 26
(5) Multidomain + placebo, high MMSE operationalized as MMSE score 30
(6) Multidomain + PUFA, high MMSE operationalized as MMSE score 30

Analysis 7.2. Comparison 7: Subgroup analyses, Outcome 2: Subgroup analysis 2. Participants at increased risk, defined by ApoE4 genotype. Outcome. Cognitive decline

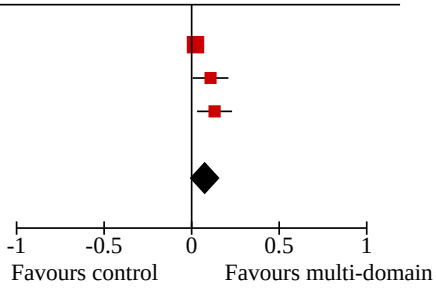
Study or Subgroup	MD	SE	Multi-domain Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
7.2.1 Carrier						
FINGER 2015	0.074	0.062	173	189	16.8%	0.07 [-0.05 , 0.20]
MAPT 2017 (1)	0.24	0.101	71	38	6.8%	0.24 [0.04 , 0.44]
MAPT 2017 (2)	0.201	0.101	76	38	6.8%	0.20 [0.00 , 0.40]
Subtotal (95% CI)			**320**	**265**	**30.5%**	**0.14 [0.04 , 0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 2.47, df = 2 (P = 0.29); I² = 19%						
Test for overall effect: Z = 2.69 (P = 0.007)						
7.2.2 Noncarrier						
FINGER 2015	0.03	0.043	380	367	31.2%	0.03 [-0.05 , 0.11]
MAPT 2017 (2)	0.048	0.057	242	118	19.5%	0.05 [-0.06 , 0.16]
MAPT 2017 (1)	0.053	0.058	233	118	18.9%	0.05 [-0.06 , 0.17]
Subtotal (95% CI)			**855**	**603**	**69.5%**	**0.04 [-0.02 , 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Total (95% CI)			**1175**	**868**	**100.0%**	**0.07 [0.02 , 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 5.61, df = 5 (P = 0.35); I² = 11%						
Test for overall effect: Z = 2.64 (P = 0.008)						
Test for subgroup differences: Chi² = 2.87, df = 1 (P = 0.09), I² = 65.2%						



Footnotes
(1) Multidomain + PUFA
(2) Multidomain + placebo

Analysis 7.3. Comparison 7: Subgroup analyses, Outcome 3: Subgroup analysis 3. Participants at increased risk, defined by CAIDE score on baseline > 6. Outcome. Cognitive decline

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Random, 95% CI
FINGER 2015	0.022	0.01	46.5%	0.02 [0.00 , 0.04]
MAPT 2017 (1)	0.108	0.052	26.5%	0.11 [0.01 , 0.21]
MAPT 2017 (2)	0.131	0.051	27.0%	0.13 [0.03 , 0.23]
Total (95% CI)			**100.0%**	**0.07 [-0.00 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 6.80, df = 2 (P = 0.03); I² = 71%				
Test for overall effect: Z = 1.85 (P = 0.06)				
Test for subgroup differences: Not applicable				



Footnotes
(1) Multidomain + placebo
(2) Multidomain + PUFA

ADDITIONAL TABLES

Table 1. Overview of included studies

Study	Study size	Characteristics of participants	Age at baseline	Targeted domains	Intervention duration	Follow-up
DR's EXTRA 2010	1410	Unselected community-dwelling participants	Mean 65.9 years	Physical activity, diet	2 years	2 years
FINGER 2015	1260	Community-dwelling participants with CAIDE score > 6	Mean 69.3	Diet, physical exercise, cognitive training, social activities, management of metabolic and vascular risk factors	2 years	2 years
HATICE 2019	2724	Community-dwelling participants with two or more vascular risk factors	Median 69 years	Smoking, blood pressure, cholesterol, diabetes, weight, physical activity, and nutrition	18 months	18 months
Lee 2014	1115	Unselected community-dwelling participants	Mean 77.1 years	Physical activity, cognitive and social activities, alcohol, smoking, lean body mass and healthy diet	18 months	18 months
Li 2018	510	Mine-workers with history of hypertension	Mean 45.6 years	Lifestyle, nutrition, hypertension, physical activity, smoking cessation, weight loss, alcohol, mental stress	2 years	2 years
Look AHEAD 2017	5145	Community-dwelling participants with diabetes	Mean 58.8 years	Weight loss, physical activity	10 years	10-13 years
MAPT 2017	1680	Community-dwelling participants with memory complaints	Mean 75.3 years	Cognitive stimulation, physical activity, and nutrition, management of cardiovascular risk factors and functional impairments	3 years	3 years
preDIVA 2016	3526	Unselected community-dwelling participants	Mean 74.5 years	Smoking, diet, physical activity, weight, blood pressure, diabetes, dyslipidaemia.	6 years	6-8 years
Taiwan Health 2020	1082	Community-dwelling participants with memory complaints	Mean 75.1 years	Physical exercise, cognitive training, nutrition advice, disease education	1 year	1 year

CAIDE: Cardiovascular Risk Factors, Aging, and Incidence of Dementia

APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved

(Continued)

1. CENTRAL (The Cochrane Library) http://cr-so.cochrane.org/SearchSim-ple.php [Most recent search for this review: 28 April 2021]	#1 MESH DESCRIPTOR Dementia EXPLODE ALL TREES 5587 #2 MESH DESCRIPTOR Delirium EXPLODE ALL TREES 695 #3 MESH DESCRIPTOR Wernicke Encephalopathy EXPLODE ALL TREES 4 #4 MESH DESCRIPTOR Neurocognitive Disorders EXPLODE ALL TREES 10412 #5 MESH DESCRIPTOR Cognitive Dysfunction EXPLODE ALL TREES 1248 #6 dement*:TI,AB,KY 11728 #7 alzheimer*:TI,AB,KY 10368 #8 (lewy* adj2 bod*):TI,AB,KY 359 #9 (chronic adj2 cerebrovascular):TI,AB,KY 109 #10 ("organic brain disease" or "organic brain syndrome"):TI,AB,KY 134 #11 (benign senescent forgetfulness):TI,AB,KY 2 #12 (cerebr* adj2 deteriorat*):TI,AB,KY 10 #13 (cerebral* adj2 insufficient*):TI,AB,KY 1 #14 ("major neurocognitive disorder*" or "Cognitive Impairment and Disability"):TI,AB,KY 90 #15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 22642 #16 multidomain:TI,AB,KY 197 #17 multi-domain:TI,AB,KY 127 #18 Multi-component:TI,AB,KY 1051 #19 Multicomponent:TI,AB,KY 1565 #20 MESH DESCRIPTOR Combined Modality Therapy EXPLODE ALL TREES 20769 #21 (multi* adj3 domain*):TI,AB,KY 511 #22 (Multi* adj3 component*):TI,AB,KY 1357 #23 MESH DESCRIPTOR Exercise EXPLODE ALL TREES 23174 #24 MESH DESCRIPTOR Exercise Therapy EXPLODE ALL TREES 12827 #25 (Interval Train*):TI,AB,KY 2086 #26 (Physical activit*):TI,AB,KY 27231 #27 (Physical train*):TI,AB,KY 1721 #28 (Physical Therap*):TI,AB,KY 9049 #29 Exercis*:TI,AB,KY 92975 #30 (physical fitness):TI,AB,KY 4395 #31 MESH DESCRIPTOR Diet EXPLODE ALL TREES 17383 #32 MESH DESCRIPTOR Vitamins EXPLODE ALL TREES 18476	APRIL 2020: 3481 APRIL 2021: 679

(Continued)

	#33 MESH DESCRIPTOR Minerals EXPLODE ALL TREES 3744 #34 MESH DESCRIPTOR Dietary Supplements EXPLODE ALL TREES 11719 #35 MESH DESCRIPTOR Calcium Carbonate EXPLODE ALL TREES 645 #36 vitamin*:TI,AB,KY 28510 #37 diet*:TI,AB,KY 83134 #38 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 230476 #39 #15 AND #38 3481	
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [Most recent search for this review: 28 April 2021]	1 exp Dementia/ 2 Delirium/ 3 Wernicke Encephalopathy/ 4 Delirium, Dementia, Amnestic, Cognitive Disorders/ or Cognitive Dysfunction/ 5 dement*.mp. 6 alzheimer*.mp. 7 (lewy* adj2 bod*).mp. 8 (chronic adj2 cerebrovascular).mp. 9 ("organic brain disease" or "organic brain syndrome").mp. 10 "benign senescent forgetfulness".mp. 11 (cerebr* adj2 deteriorat*).mp. 12 (cerebral* adj2 insufficient*).mp. 13 ("major neurocognitive disorder*" or "Cognitive Impairment and Disability").ti,ab. 14 or/1-13 15 multidomain.ti,ab. 16 "multi-domain".ti,ab. 17 "Multi-component".ti,ab. 18 "Multicomponent".ti,ab. 19 exp Combined Modality Therapy/ 20 (multi* adj3 domain*).ti,ab. 21 (Multi* adj3 component*).ti,ab. 22 exp Exercise/ 23 exp Exercise Therapy/ 24 "Interval Train*".ti,ab. 25 "Physical activit*".ti,ab.	APRIL 2020: 2617 APRIL 2021: 465

(Continued)

26 "Physical train*".ti,ab.

27 "Physical Therap*".ti,ab.

28 Exercis*.ti,ab.

29 "physical fitness".ti,ab.

30 exp Diet/

31 exp Vitamins/

32 exp Minerals/

33 exp Dietary Supplements/

34 Calcium Carbonate/

35 vitamin*.ti,ab.

36 diet*.ti,ab.

37 or/15-36

38 14 and 37

39 exp Secondary Prevention/

40 exp Primary Prevention/

41 "delay onset".ti,ab.

42 ((cognit* or cognition or memory or mental or brain) adj3 (impair* or decline* or deficit* or loss or lose or stop* or reduc*)).ti,ab.

43 prevent*.ti,ab.

44 taper*.ti,ab.

45 avoid*.ti,ab.

46 "cut* down".ti,ab.

47 or/39-46

48 38 and 47

49 randomized controlled trial.pt.

50 controlled clinical trial.pt.

51 randomized.ab.

52 placebo.ab.

53 drug therapy.fs.

54 randomly.ab.

55 trial.ab.

56 groups.ab.

57 or/49-56

58 exp animals/ not humans.sh.

59 57 not 58

(Continued)

	60 48 and 59	
3. Embase 1974 to present (Ovid SP) [Most recent search for this review: 28 April 2021]	1 Dementia/ 2 Delirium/ 3 Wernicke Encephalopathy/ 4 Delirium, Dementia, Amnestic, Cognitive Disorders/ 5 ("benign senescent forgetfulness" or ("normal pressure hydrocephalus" and "shunt*") or ("organic brain disease" or "organic brain syndrome") or ((cerebral* or cerebrovascular or cerebro-vascular) adj2 insufficien*) or (cerebr* adj2 deteriorat*) or (chronic adj2 (cerebrovascular or cerebro-vascular)) or (creutzfeldt or jcd or cjd) or (lewy* adj2 bod*) or (pick* adj2 disease) or alzheimer* or binswanger* or deliri* or dement* or huntington* or korsako*).tw. 6 "major neurocognitive disorder".ti,ab. 7 or/1-6 8 multidomain.ti,ab. 9 "multi-domain".ti,ab. 10 "Multi-component".ti,ab. 11 "Multicomponent".ti,ab. 12 exp Combined Modality Therapy/ 13 (multi* adj3 domain*).ti,ab. 14 (Multi* adj3 component*).ti,ab. 15 exp exercise/ 16 exp kinesiotherapy/ 17 "Interval Train*".ti,ab. 18 "Physical activit*".ti,ab. 19 "Physical train*".ti,ab. 20 "Physical Therap*".ti,ab. 21 Exercis*.ti,ab. 22 "physical fitness".ti,ab. 23 exp diet/ 24 exp vitamin/ 25 exp mineral/ 26 exp dietary supplement/ 27 exp calcium carbonate/ 28 vitamin*.ti,ab. 29 diet*.ti,ab. 30 or/8-29	APRIL 2020: 4449 APRIL 2021: 898

(Continued)

	31 7 and 30 32 exp secondary prevention/ 33 exp primary prevention/ 34 "delay onset".ti,ab. 35 ((cognit* or cognition or memory or mental or brain) adj3 (impair* or decline* or deficit* or loss or lose or stop* or reduc*)).ti,ab. 36 prevent*.ti,ab. 37 taper*.ti,ab. 38 avoid*.ti,ab. 39 "cut* down".ti,ab. 40 or/32-39 41 31 and 40 42 randomized controlled trial/ 43 controlled clinical trial/ 44 random$.ti,ab. 45 randomization/ 46 intermethod comparison/ 47 placebo.ti,ab. 48 (compare or compared or comparison).ti. 49 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 50 (open adj label).ti,ab. 51 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 52 double blind procedure/ 53 parallel group$1.ti,ab. 54 (crossover or cross over).ti,ab. 55 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 56 (assigned or allocated).ti,ab. 57 (controlled adj7 (study or design or trial)).ti,ab. 58 (volunteer or volunteers).ti,ab. 59 trial.ti. 60 or/42-59 61 41 and 60	
4. PsycINFO (Ovid SP)	1 exp Dementia/	APRIL 2020: 1017

(Continued)

[Most recent search for this review: 28 April 2021]	2 exp Delirium/	APRIL 2021: 142
	3 exp Huntingtons Disease/	
	4 exp Kluver Bucy Syndrome/	
	5 exp Wernickes Syndrome/	
	6 exp Cognitive Impairment/	
	7 dement*.mp.	
	8 alzheimer*.mp.	
	9 (lewy* adj2 bod*).mp.	
	10 deliri*.mp.	
	11 (chronic adj2 cerebrovascular).mp.	
	12 ("organic brain disease" or "organic brain syndrome").mp.	
	13 "supranuclear palsy".mp.	
	14 ("normal pressure hydrocephalus" and "shunt*").mp.	
	15 "benign senescent forgetfulness".mp.	
	16 (cerebr* adj2 deteriorat*).mp.	
	17 (cerebral* adj2 insufficient*).mp.	
	18 (pick* adj2 disease).mp.	
	19 (creutzfeldt or jcd or cjd).mp.	
	20 huntington*.mp.	
	21 binswanger*.mp.	
	22 korsako*.mp.	
	23 ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp.	
	24 "major neurocognitive disorder".ti,ab.	
	25 or/1-24	
	26 multidomain.ti,ab.	
	27 "multi-domain".ti,ab.	
	28 "Multi-component".ti,ab.	
	29 "Multicomponent".ti,ab.	
	30 (multi* adj3 domain*).ti,ab.	
	31 (Multi* adj3 component*).ti,ab.	
	32 exp Exercise/	
	33 "Interval Train*".ti,ab.	
	34 "Physical activit*".ti,ab.	
	35 "Physical train*".ti,ab.	

(Continued)

	36 "Physical Therap*".ti,ab. 37 Exercis*.ti,ab. 38 "physical fitness".ti,ab. 39 exp Diets/ 40 exp Vitamins/ 41 exp Dietary Supplements/ 42 vitamin*.ti,ab. 43 diet*.ti,ab. 44 or/26-43 45 25 and 44 46 exp Prevention/ 47 "delay onset".ti,ab. 48 ((cognit* or cognition or memory or mental or brain) adj3 (impair* or decline* or deficit* or loss or lose or stop* or reduc*)).ti,ab. 49 prevent*.ti,ab. 50 taper*.ti,ab. 51 avoid*.ti,ab. 52 "cut* down".ti,ab. 53 or/46-52 54 45 and 53 55 exp Clinical Trials/ 56 randomly.ab. 57 randomi?ed.ti,ab. 58 placebo.ti,ab. 59 groups.ab. 60 "double-blind*".ti,ab. 61 "single-blind*".ti,ab. 62 RCT.ti,ab. 63 or/55-62 64 54 and 63	
5. CINAHL (EBSCOhost) [Most recent search for this review: 28 April 2021]	S63 S52 AND S62 S62 S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 S61 (MH "Random Assignment") S60 (MH "Single-Blind Studies") or (MH "Double-Blind Studies") or (MH "Triple-Blind Studies")	APRIL 2020: 492 APRIL 2021: 58

(Continued)

S59 (MH "Crossover Design")

S58 (MH "Factorial Design")

S57 (MH "Placebos")

S56 (MH "Clinical Trials")

S55 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study"

S54 TX crossover OR "cross-over"

S53 TX "latin square"

S52 S44 AND S51

S51 S45 OR S46 OR S47 OR S48 OR S49 OR S50

S50 TX cut* down

S49 TX avoid*

S48 TX taper*

S47 TX prevent*

S46 TX (cognit* or cognition or memory or mental or brain) N3 (impair* or decline* or deficit* or loss or lose or stop* or reduc*)

S45 TX "delay onset"

S44 S20 AND S43

S43 S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42

S42 TX diet*

S41 TX vitamin*

S40 (MH "Calcium Carbonate")

S39 (MH "Dietary Supplements+")

S38 (MH "Minerals+")

S37 (MH "Vitamins+")

S36 (MH "Diet+")

S35 TX physical fitness

S34 TX Exercis*

S33 TX Physical Therap*

S32 TX Physical train*

S31 TX Physical activit*

S30 TX Interval Train*

S29 (MH "Therapeutic Exercise+")

S28 (MH "Exercise+")

(Continued)

	S27 TX Multi* N3 component* S26 TX multi* N3 domain* S25 (MH "Combined Modality Therapy+") S24 TX Multicomponent S23 TX Multi-component S22 TX multi-domain S21 TX multidomain S20 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 S19 TX "major neurocognitive disorder" S18 TX korsako* S17 TX binswanger* S16 TX huntington* S15 TX creutzfeldt or jcd or cjd S14 TX pick* N2 disease S13 TX cerebral* N2 insufficient* S12 TX cerebr* N2 deteriorat* S11 TX "benign senescent forgetfulness" S10 TX "normal pressure hydrocephalus" and "shunt*" S9 TX "organic brain disease" or "organic brain syndrome" S8 TX chronic N2 cerebrovascular S7 TX deliri* S6 TX lewy* N2 bod* S5 TX alzheimer* S4 TX dement* S3 (MH "Wernicke's Encephalopathy") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S1 (MH "Dementia+")	
6. ISI Web of Science – core collection [Most recent search for this review: 28 April 2021]	TOPIC: (dement* OR alzheimer* OR "vascular cognitive impairment" OR "lew* bod*" OR CADASIL OR "cognit* impair*" OR FTD OF FTLD OR "cerebrovascular insufficienc*" OR AD OR VCI) AND TOPIC: (randomly OR randomised OR randomized OR "random allocat*" OR RCT OR CCT OR "double blind*" OR "single blind*" OR "double blind*" OR "single blind*" OR trial) AND TOPIC: (multidomain OR multi-domain OR Multi-component OR Multicomponent OR Combined Modality Therapy)	APRIL 2020: 514 APRIL 2021: 140
7. LILACS (BIREME)	alzheimer OR alzheimers OR alzheimer's OR dementia OR demenc$ [Words] and randomly OR randomised OR randomized OR RCT OR "controlled trial"	APRIL 2020: 1

(Continued)

[Most recent search for this review: 28 April 2021]	OR "double blind$" OR placebo [Words] and multidomain OR multi-domain OR Multi-component OR Multicomponent OR Combined Modality Therapy [Words]	APRIL 2021: 0
8. ClinicalTrials.gov (www.clinicaltrials.gov) [Most recent search for this review: 28 April 2021]	dementia OR alzheimers OR cognition OR cognitive | multidomain OR multi-domain OR Multi-component OR Multicomponent OR Combined Modality	APRIL 2020: 89 APRIL 2021: 26
9. CDCIG specialised register (CRS web) [Most recent search for this review: 28 April 2021]	multidomain OR multi-domain OR Multi-component OR Multicomponent OR Combined Modality	APRIL 2020: 379 APRIL 2021: 119
10. ICTRP [Most recent search for this review: 28 April 2021]	dementia OR alzheimers OR cognition OR cognitive | multidomain OR multi-domain OR Multi-component OR Multicomponent OR Combined Modality	APRIL 2021: 50
TOTAL before de-duplication		APRIL 2020: 13039 APRIL 2021: 2577
TOTAL after de-duplication		APRIL 2020: 9206 APRIL 2021: 1929
TOTAL after Cochrane's Screen4Me process (using RCT machine learning classifier and Cochrane Crowd)		APRIL 2020: **3609**
TOTAL after first assessment by CDCIG information specialist		APRIL 2020: **1321**

HISTORY

Protocol first published: Issue 4, 2020

CONTRIBUTIONS OF AUTHORS

Melanie Hafdi (MH): conceiving and designing the review, coordinating the review, study selection, data extraction, data entry into RevMan Web, risk of bias assessment for the included studies, data interpretation and assessment of the certainty in the body of evidence, writing of the review
Marieke Hoevenaar-Blom (MH-B): conceiving and designing the review, study selection, data extraction, verification of data entry into RevMan web, risk of bias assessment for the included studies, data interpretation and assessment of the certainty in the body of evidence, critical revision of manuscript
Edo Richard (ER): conceiving and designing the review, data interpretation, critical revision of manuscript

DECLARATIONS OF INTEREST

MH: None were stated

MH-B: Was one of two authors who extracted outcome data but was closely involved in the preDIVA and HATICE study. To ensure objective data extraction, we brought in a third adjudicator (MPW; Acknowledgements) to independently extract and assess all outcome data.

ER: None were stated

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- Donders Institute of Brain, Behaviour and Cognition, Radboud University Medical Centre, Netherlands

  Employer review authors

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our protocol (Hafdi 2020), we predefined several trial characteristics as of interest for exploring possible reasons for heterogeneity. We intended to carry out these subgroup analyses if at least two studies were available for each subgroup and if statistical heterogeneity was suggested (I^2 of 40% or more). We did not carry out the following subgroup analyses due to no or limited available studies: duration of intervention > 24 months; pharmacological interventions versus mixed versus non pharmacological interventions. We did not carry out a subgroup analysis for interventions including cognitive training because no statistical heterogeneity was found (Analysis 3.2, I^2 = 0%). We did not carry out the following sensitivity analyses due to no available studies: exclusion of studies not using internationally accepted definitions for MCI or dementia; inclusion of studies that are registered in a trial register but have not yet been published; replacing original follow-up with extended follow-up; stratification according to age for the outcomes of incidence of dementia and MCI; exclusion of studies with < 5 years of follow-up and incident dementia as primary outcome measure.

We also planned to graphically explore reporting bias in funnel plot analyses, however, as the Cochrane Handbook advises assessing funnel plot asymmetry only if at least 10 studies are included in the meta-analysis, we omitted this analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Cognition; *Cognitive Dysfunction; *Dementia [prevention & control]; Quality of Life

MeSH check words

Aged; Humans